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Synthesis of pyranicin and its deoxygenated analogues and their inhibitory action with bovine heart mitochondrial complex I

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ABSTRACT

Total synthesis of pyranicin and its deoxygenated analogues was achieved using $Cl_2Pd(CH_3CN)_2$ catalyzed diastereoselective cyclization of the allylic ester as the key step. The inhibitory activity of these compounds for mitochondrial NADH–ubiquinone oxidoreductase (complex I) was poorer than those of ordinary mono-THF acetogenins such as annonacin.

1. Introduction

The annonaceous acetogenins, which are isolated from a number of tropical plants of *Annonaceae*, have attracted much attention in recent years due to a wide variety of biological features, including cytotoxic, antitumoral, and antimalarial activities. Their unique structures are characterized by a terminal α,β-unsaturated γ-lactone ring and a long aliphatic side chain, which is connected with various oxygen containing moieties such as THF, THP, and/or epoxide rings, and several hydroxy groups on C-35 or C-37 carbon chain. The inhibitory effect of acetogenins on mitochondrial NADH–ubiquinone oxidoreductase (complex I) is of particular importance since their diverse biological activities are thought to be attributable to this effect. Using systematically selected natural and synthetic THF- type acetogenins, Miyoshi and co-workers revealed that the alkyl spacer linking the γ-lactone and the hydroxylated THF moieties dynamically regulate the binding of these two toxophores to the putative binding sites.[1] So far, over 430 acetogenins have been isolated from *Annonaceae*,[2–4] however, only 8 compounds contain a THP ring. Consequently, significant efforts have been devoted toward synthesis of THP-containing acetogenins due to their unique structures.[5] Pyranicin (**1**) is a mono-THP acetogenin, first isolated from the stem bark of *Goniothalamus giganteus* in 1998 (Fig. 1).[6] In 2003, Takahashi synthesized pyranicin (**1**) via SmI_2-induced reductive cyclization of β-alkoxy acrilate.[5f] Strand also achieved synthesis of pyranicin (**1**) using asymmetric Horner–Emmons reaction in 2005.[5c,d] To our knowledge, the inhibitory action of THP-type acetogenins has not been characterized at the enzyme level. Pyranicin (**1**) has a C-13 alkyl spacer whose length is most suitable for the inhibition of complex I in the case of mono- and bis-THF acetogenins.[1] Thus, it is very important to investigate the role of the THP ring in the inhibitory action. In the previous communication, we reported the total synthesis of pyranicin (**1**) employing a Pd-catalyzed diastereoselective cyclization strategy,[7,8] and its inhibitory action with bovine heart complex I.[9] As for the inhibitory activity, the IC_{50} of pyranicin was 7.5 (±0.30) nM. This indicated that the inhibitory potency of this compound is slightly, but significantly, lower than that of *cis*-solamin (IC_{50} 2.2 (±0.18) nM).[10] Considering the fact that the presence of multiple hydroxy groups in the spacer region is markedly adverse to the inhibition,[1a] the presence of an additional hydroxy group in the 10-position may be the cause of the decrease in the inhibitory potency of pyranicin. In order to elucidate the role of the THP ring, we designed deoxygenated pyranicin analogues, 10-deoxypyranicin (**2**)

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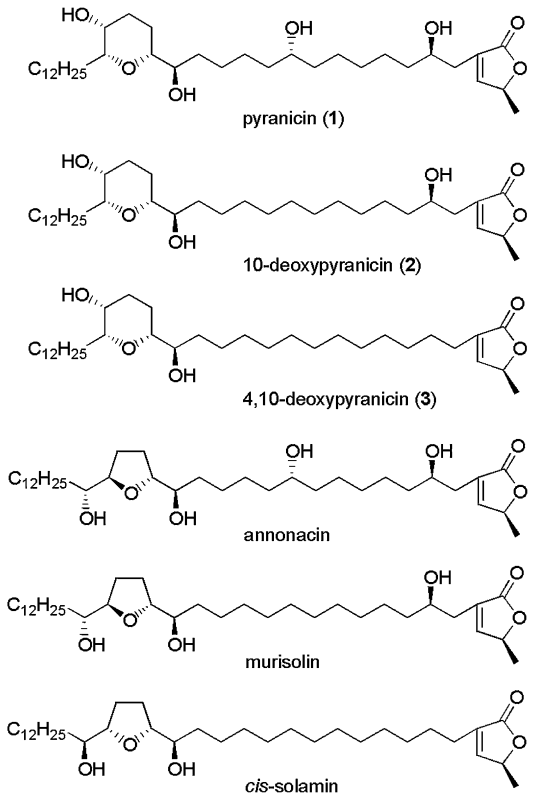


Figure 1. The structures of pyranicin (**1**) and its deoxygenated analogues, 10-deoxypyranicin (**2**), 4,10-dideoxypyranicin (**3**), and related mono-THF acetogenins, annonacin, murisolin, and *cis*-solamin.

and 4,10-dideoxypyranicin (**3**) to make direct comparison with mono-THF acetogenins, annonacin,[11] murisolin,[12] and *cis*-solamin (Fig. 1). Herein we wish to report the synthesis of **1**, **2**, and **3** and their inhibitory action with bovine heart mitochondrial complex I.

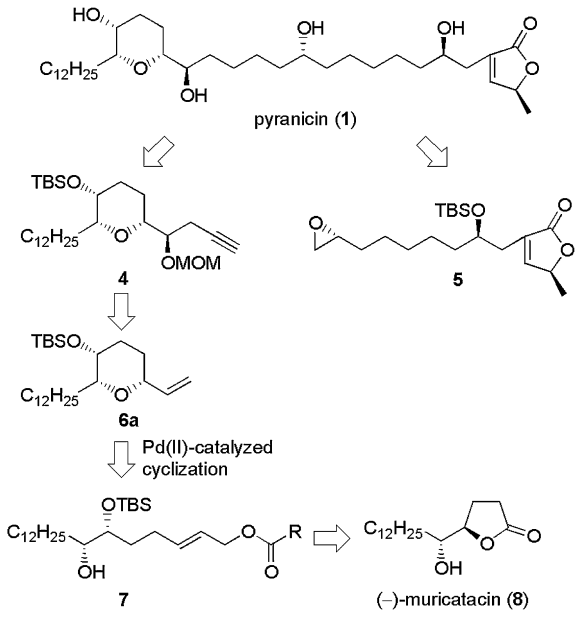
2. Results and discussion

2.1. Synthesis

Scheme 1 outlines our synthetic strategy of pyranicin (**1**). The key step is Pd-catalyzed diastereoselective cyclization from **7** to **6a**. This reaction proceeded in high diastereoselective manner and it would be useful for the synthesis of other THP-containing acetogenins. The starting material is (−)-muricatacin (**8**), which was reported by our group.[13,14]

As shown in Scheme 2, the key intermediate **7** was constructed as follows. Protection of **8** with ethyl vinyl ether and a catalytic amount of PPTS afforded **9**, followed by semi-reduction with DIBALH afforded hemi-acetal and subsequent careful Horner–Emmons reaction at −50 °C afforded α,β-unsaturated ester **10**. Protection of the hydroxy group of **10** with TBSCl and imidazole to give **11** and subsequent reduction with DIBALH gave allylic alcohol **12**. Esterification of **12** with various acid chlorides, followed by removal of the ethoxyethyl group with 0.5 N hydrochloric acid afforded the cyclization precursor **7** (Scheme 2).

The results of diastereoselective cyclization of **7** are summarized in Table 1. While $Cl_2Pd(CH_3CN)_2$ was the most effective catalyst in the diastereoselective cyclization, $PdCl_2$ and $Cl_2Pd(PPh_3)_2$ were ineffective. One of the reasons for low selectivity and yield in the case of $PdCl_2$ may be due to the low solubility in organic solvent. Because $PdCl_2$ exists as an essentially linear doubly Cl-bridged polymer.[15] As far as we have found, substituted aromatic esters are



Scheme 1. Retrosynthetic analysis.

appropriate substrates such as 3-phenylbenzoate. As for the solvent, CH_2Cl_2 gave a good selectivity although the yield was a little bit lower than DME. A chair-like transition state with an equatorial orientation of all substituents can explain the favorable formation of the desired stereoisomer **6a**. Steric requirement such as 3-phenylbenzoyl group might also be necessary to get high selectivity (Fig. 2).

Determination of the relative stereochemistry of **6a** was performed by 2D-NOESY experiment of **6a′**, which was afforded by deprotection of the TBS group of **6a** with TBAF. On the other hand, the correlation between the C-2 and C-6 proton of **6b′** was not observed in 2D-NOESY experiment (Fig. 3).

Diastereoselective dihydroxylation of **6a** by the Sharpless procedure using $(DHQD)_2AQN$ as a ligand gave **14** in 84% de.[16] The undesired diastereomer was removed by silica gel column chromatography at this stage.

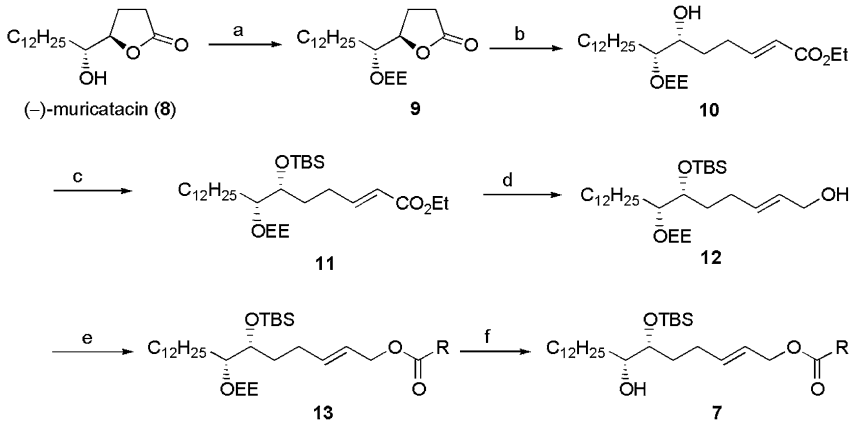
Silylation of the hydroxy group of **14** with TBSCl, Et_3N, and DMAP to give **15** and subsequence treatment with tetrabutylammonium fluoride furnished terminal epoxide **16**. Alkynylation of **16** with lithium acetylide an ethylenediamine complex to afford **17** followed by protection of the corresponding hydroxy group with MOMBr and *i*-Pr_2NEt furnished tetrahydropyran moiety **4** (Scheme 3).

The γ-lactone moiety was prepared by Keinan's method[17] with Jacobsen's hydrolytic kinetic resolution.[18,19] Terminal olefin **18** was constructed as we have reported earlier, starting from 1,8-nonadiene.[12b] Olefin **18** was converted to epoxide **19** using *m*CPBA. Jacobsen's hydrolytic kinetic resolution of **19** gave γ-lactone moiety **5**, with an *R* configuration at the C-8 position (Scheme 4).

Both segments **4** and **5** were coupled by the reported procedure at 75% yield,[20,21] followed by diimide reduction with *p*-$TsNHNH_2$ and sodium acetate in ethylene glycol–diethyl ether.[22] Finally, deprotection of the TBS and MOM ether with $BF_3 \cdot Et_2O$ afforded **1** (Scheme 5).

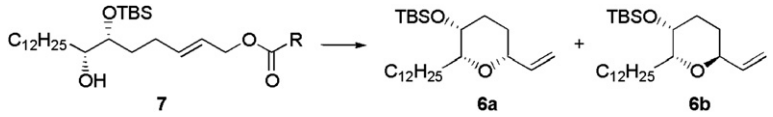
The spectroscopic data (^1H NMR, ^{13}C NMR, IR, and MS spectra) of synthetic **1** were in good agreement with those of natural and synthetic pyranicins.[5c,d,f,6] The specific rotation value was consistent with that of synthetic **1**, which was reported by Takahashi, who reported that natural and synthetic pyranicins were incompatible.[5f]

Scheme 6 outlines the synthesis of **2**. The THP part **6a** was constructed as described in Scheme 3. The α,β-unsaturated lactone **21** was prepared by following the literature.[12b] The segments **6a**



Scheme 2. Preparation of cyclization precursor **7**. Reagents and conditions: (a) ethyl vinyl ether, PPTS, CH_2Cl_2 (quant.); (b) (i) DIBALH, CH_2Cl_2, (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −50 °C (88%, two steps); (c) TBSCl, imidazole, DMF (93%); (d) DIBALH, CH_2Cl_2 (97%); (e) 3-phenylbenzoylchloride, DMAP, pyridine (96%); (f) 0.5 N HCl, THF–H_2O (85%).

Table 1
Pd(II)-catalyzed diastereoselective cyclization of allylic esters.



R	Solvent	Catalyst	Time (h)	Temp. (°C)	Yield (**6a**+**6b**) %	**6a**:**6b**[a]
Mesityl	DME	$Cl_2Pd(PPh_3)_2$	12	rt	—	—
Mesityl	DME	$PdCl_2$	12	rt	49	78:22
Mesityl	DME	$Cl_2Pd(CH_3CN)_2$	12	rt	73	84:16
Mesityl	DME	$Cl_2Pd(CH_3CN)_2$	12	rt	78	67:33
t-Bu	DME	$Cl_2Pd(CH_3CN)_2$	12	rt	23	81:19
Phenyl	DME	$Cl_2Pd(CH_3CN)_2$	12	rt	29	83:17
Biphenyl	DME	$Cl_2Pd(CH_3CN)_2$	12	rt	99	90:10
Biphenyl	DME	$Cl_2Pd(CH_3CN)_2$	12	0	N.R	—
Biphenyl	CH_2Cl_2	$Cl_2Pd(CH_3CN)_2$	4	−10	74	93:7

[a] The ratio of **6a** and **6b** was determined by ^1H NMR analysis.

and **21** were coupled by the Sonogashira cross-coupling reaction to afford enyne **22** in 51% yield.[23] Diimide reduction with *p*-$TsNHNH_2$ and sodium acetate in ethylene glycol–diethyl ether afforded **23**. Finally, deprotection of the TBS and MOM ether with $BF_3\cdot Et_2O$ afforded **2** (Scheme 6).

Compound **3** was constructed as follows. The THP part **4** was constructed as described in Scheme 3. The lactone **24** was synthesized by following the literature procedure from 1,7-heptanediol.[24] The segments **4** and **24** were coupled by the Sonogashira cross-coupling reaction to afford enyne **25** in 67% yield.[23] Diimide reduction with *p*-$TsNHNH_2$ and sodium acetate in ethylene glycol–diethyl ether followed by deprotection of the TBS and MOM ether with $BF_3\cdot Et_2O$ afforded **3** (Scheme 7).

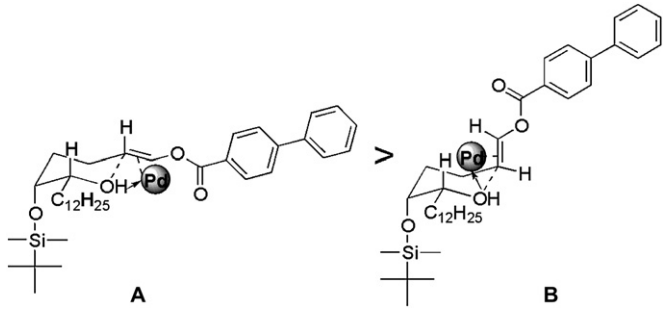


Figure 2.

2.2. Inhibitory action with bovine heart mitochondrial complex I

Compounds **1**, **2**, and **3** on bovine heart mitochondrial complex I were tested as inhibitors of bovine heart mitochondrial complex I.[1a] Bullatacin, one of the most potent natural acetogenins, was used as a control; the IC_{50} value used, a measure of inhibitory potency, was 0.83±0.06 nM.[1b] Under the same conditions, IC_{50} values of **1**, **2**, and **3** were 7.5±0.30, 3.0±0.18, and 31±0.06 nM, respectively. The IC_{50}

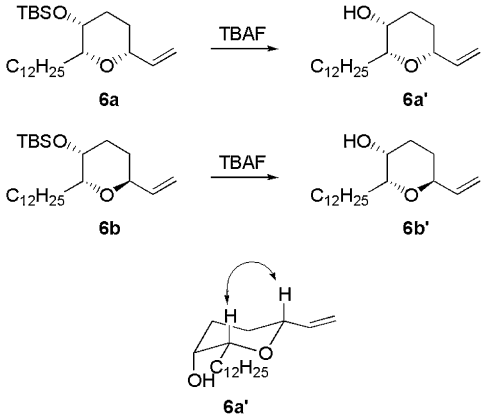
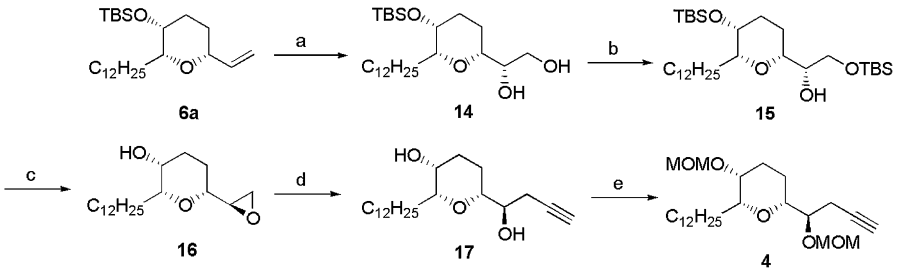
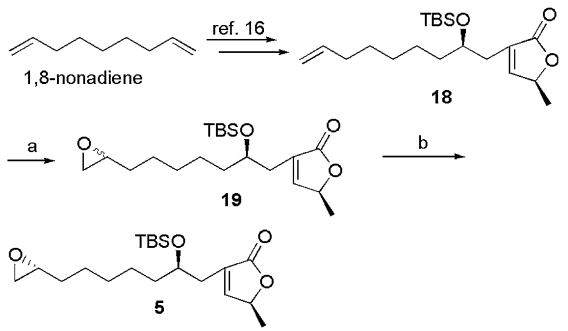


Figure 3. Determination of the relative stereochemistry of **6a** using 2D-NOESY correlations.



Scheme 3. Synthesis of THP part of **4**. Reagents and conditions: (a) $(DHQD)_2AQN$, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH/H_2O, (95%, 84% de); (b) TBSCl, Et_3N, DMAP, CH_2Cl_2 (98%); (c) (i) MsCl, Et_3N, CH_2Cl_2, (ii) TBAF, THF (85%, two steps); (d) lithium acetylide, an ethylenediamine complex (84%); (e) MOMBr, *i*-Pr_2NEt (77%).

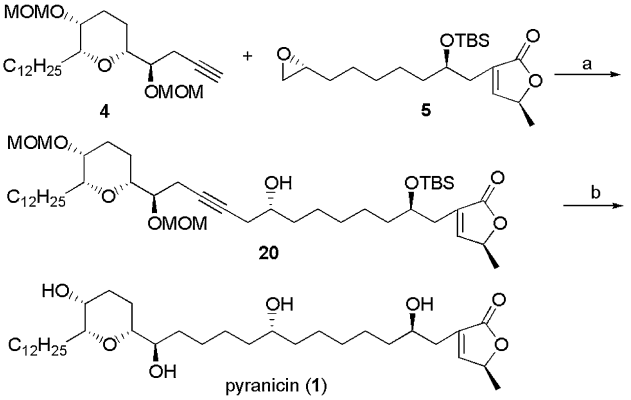


Scheme 4. Synthesis of γ-lactone part. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2 (87%); (b) (*R*,*R*)-(salen)-Co^{III}(OAc), H_2O (43%).

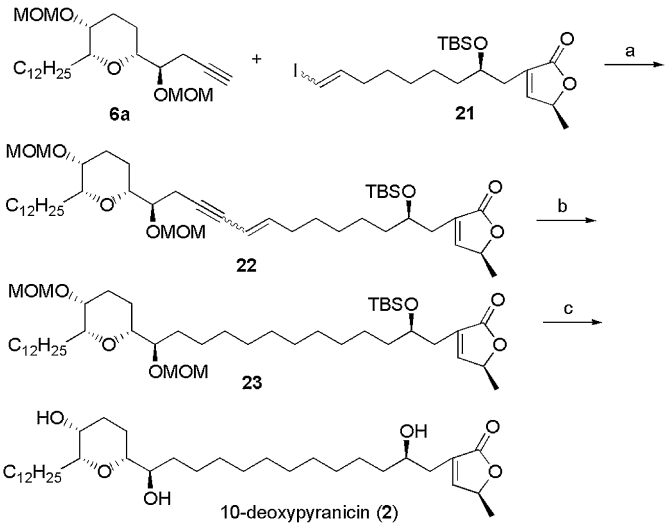
values of **1** and **2** were slightly larger than those of annonacin (3.8 nM)[1a] and murisolin (1.8±0.10 nM),[12b] respectively. Under the same experimental conditions, the IC_{50} values of **3** were significantly larger than that of *cis*-solamin (2.2±0.18 nM).[10b,25] Recently, Miyoshi and co-workers found that both the THF and the γ-lactone rings have to occupy simultaneously the two putative binding sites in the enzyme when acetogenins exhibit inhibition.[1c] If the hydroxylated THF ring moiety is replaced to the hydroxylated THP ring, conformation of the alkyl spacer and the hydroxy group in the vicinity of THP ring is drastically changed. Thus, the binding affinity of the toxophore might be weakened compared to THF acetogenins.

3. Conclusion

In conclusion, total synthesis of **1** and its deoxygenated analogues, **2** and **3** were achieved from (−)-muricatacin (**7**) via Pd(II) catalyzed diastereoselective cyclization. Compounds **1**, **2**, and **3** were investigated in terms of its inhibitory action with bovine heart mitochondrial complex I. The inhibitory activity of these THP-containing acetogenins on complex I was poorer than that of ordinary mono-THF acetogenins.



Scheme 5. Completion of the total synthesis of pyranicin. Reagents and conditions: (a) *n*-BuLi, $BF_3\cdot Et_2O$ (75%); (b) (i) *p*-$TsNHNH_2$, AcONa, DME–H_2O reflux, (ii) $BF_3\cdot Et_2O$, dimethyl sulfide (98%, two steps).

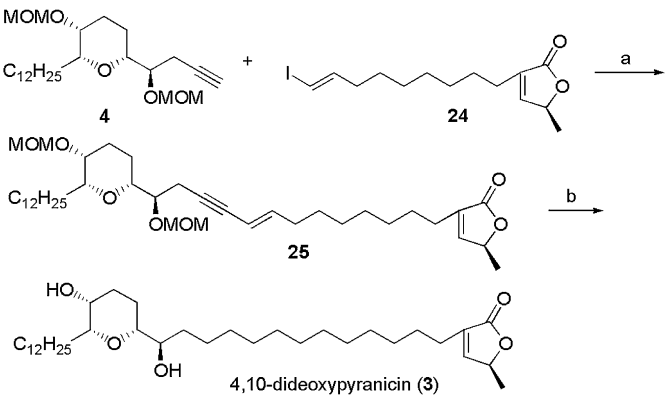


Scheme 6. Synthesis of 10-deoxypyranicin. Reagents and conditions: (a) 10 mol% $Cl_2Pd(PPh_3)_2$, CuI, Et_3N, benzene (51%); (b) *p*-$TsNHNH_2$, AcONa, DME–H_2O reflux (68%); (c) $BF_3\cdot Et_2O$, dimethyl sulfide (74%).

4. Experimental

4.1. General

All melting points were uncorrected. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX 500 FT-NMR spectrometer in $CDCl_3$ at 500 and 125 MHz, respectively. Chemical shifts were relative to tetramethylsilane as an internal standard. The coupling



Scheme 7. Synthesis of 4,10-dideoxypyranicin. Reagents and conditions: (a) 10 mol% $Cl_2Pd(PPh_3)_2$, CuI, Et_3N, benzene (67%); (b) (i) *p*-$TsNHNH_2$, AcONa, DME–H_2O reflux, (ii) $BF_3\cdot Et_2O$, dimethyl sulfide (37%, two steps).

constants were given in hertz. Mass spectra were obtained on JEOL JMS-HX211A and JMS-HX110A mass spectrometers. IR spectra were recorded with JASCO FT-IR 480 Plus infrared spectrometer. Optical rotations were determined with a JASCO DIP-1000 polarimeter.

4.1.1. (5R,1′R)-5-(1′-Ethoxyethoxytridecyl)tetrahydrofuran-2-one (**9**)

To a solution of (−)-muricatacin (**8**) (1.49 g, 5.24 mmol) in CH_2Cl_2 (30 mL) were added ethyl vinyl ether (0.60 mL, 6.29 mmol) and a catalytic amount of PPTS, stirred at room temperature for 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=5:1) to give **9** (1.86 g, quant.) as a colorless oil. IR (film): ν_{max}=2925, 2854, 1780, 1464, 1377, 1176, 1127, 1094, 1056 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=4.87 (0.5H, q, J=5.2 Hz), 4.75 (0.5H, q, J=5.2 Hz), 4.62 (0.5H, m), 4.51 (0.5H, m), 3.65–3.45 (3H, m), 2.62–2.46 (2H, m), 2.25–2.20 (1.5H, m), 2.00–1.93 (0.5H, m), 1.61–1.52 (2H, m), 1.33 (1.5H, d, J=5.0 Hz), 1.30 (1.5H, d, J=5.0 Hz), 1.35–1.22 (20H, m), 1.21 (1.5H, q, J=7.0 Hz), 1.19 (1.5H, t, J=7.0 Hz), 0.88 (3H, t, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=177.6, 177.0, 100.5, 99.2, 82.2, 80.9, 78.3, 60.9, 60.3, 31.9, 30.6, 29.9, 29.8 (2C), 29.6 (3C), 29.5 (2C), 29.3, 28.6 (2C), 25.3, 25.2, 24.3, 23.8, 22.7, 20.4, 15.3 (2C), 14.1; HREIMS [(M−Me)$^+$]: calcd for $C_{20}H_{37}O_4$, 341.2692; found, 341.2681.

4.1.2. (2E,6R,7R)-Ethyl 7-ethoxyethoxy-6-hydroxy-2-nonadecenoate (**10**)

To a solution of **9** (1.86 g, 5.24 mmol) in CH_2Cl_2 (30 mL) was added DIBALH (1.03 mL, 5.76 mmol) at −78 °C. After being stirred for 15 min at same temperature, the reaction was quenched with MeOH (5.0 mL). The mixture was warmed to room temperature and filtered through Celite and silica gel layer, and the filtrate was dried over $MgSO_4$, filtered, and concentrated. This compound was immediately used for the next step without purification. Triethylphosphonoacetate (2.16 mL, 10.5 mmol) was added to a suspension of NaH [60% in mineral oil (503 mg, 12.6 mmol)] in THF (30 mL) at 0 °C under an argon gas atmosphere and the mixture was stirred for 0.5 h. Crude hemi-acetal in THF (10 mL) was added to a solution. The mixture was stirred for 1.5 h at −50 °C. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=10:1) to give **10** (1.97 g, 88%) as a colorless oil. IR (film): ν_{max}=3448, 2925, 2854, 1722, 1655, 1466, 1369, 1267, 1156, 1128, 1096, 1052, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=6.99 (1H, m), 5.85 (1H, d, J=16 Hz), 4.75 (0.4H, q, J=5.5 Hz), 4.61 (0.6H, q, J=5.5 Hz), 4.18 (2H, m), 3.70 (0.6H, m), 3.67–3.63 (0.4H, m), 3.59–3.44 (2.6H, m), 3.39–3.36 (0.4H, m), 3.34–3.30 (0.6H, m), 2.51 (0.4H, d, J=5.5 Hz), 2.47–2.41 (1H, m), 2.38–2.27 (1H, m), 1.65–1.56 (2H, m), 1.54–1.47 (2H, m), 1.41–1.36 (2H, m), 1.35 (1.8H, d, J=5.8 Hz), 1.33 (1.2H, d, J=6.0 Hz), 1.30–1.26 (2H, m), 1.22 (1.8H, t, J=6.8 Hz), 1.21 (1.2H, t, J=7.0 Hz), 0.88 (3H, t, J=6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=166.7, 166.6, 149.0, 148.7, 121.6, 121.5, 101.4, 100.1, 83.6, 79.9, 72.3, 71.8, 61.6, 61.1, 60.1 (2C), 32.0, 31.9, 31.6, 31.5, 31.3, 29.9, 29.7, 29.6 (3C), 29.5, 29.3, 28.6, 28.2, 25.3, 25.2, 22.7, 20.4, 20.3, 15.3, 15.2, 14.2, 14.1; HREIMS [(M−OEt)$^+$]: calcd for $C_{23}H_{43}O_4$, 383.3113; found, 383.3161.

4.1.3. (2E,6R,7R)-Ethyl 6-(tert-butyldimethylsilyloxy)-7-ethoxyethoxy-2-nonadecenoate (**11**)

To a solution of **10** (1.97 g, 4.61 mmol) in CH_2Cl_2 (20 mL) were added imidazole (470 g, 6.92 mmol) and TBSCl (834 mg, 5.53 mmol). The resulting mixture was stirred at room temperature for 18 h. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=20:1) to give **11** (2.32 g, 93%) as a colorless oil. IR (film): ν_{max}=2926, 2855, 1724, 1655, 1464, 1367, 1257, 1097, 835, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=7.07–6.95 (1H, m), 5.83 (1H, d, J=16 Hz), 4.73 (0.4H, q, J=5.5 Hz), 4.65 (0.6H, q, J=5.5 Hz), 4.18 (2H, m), 3.81–3.78 (0.6H, m), 3.70–3.67 (0.4H, m), 3.65–3.42 (2.4H, m), 3.40–3.36 (0.6H, m), 2.41–2.32 (1H, m), 2.17–2.10 (1H, m), 1.79–1.69 (1H, m), 1.65–1.60 (1H, m), 1.53–1.44 (2H, m), 1.30–1.18 (29H, m), 0.89 (9H, s), 0.88 (3H, t, J=7.0 Hz), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=166.7, 166.6, 149.4, 149.2, 121.3, 121.2, 101.1, 98.9, 80.9, 78.0, 73.0, 72.2, 60.6, 60.1 (2C), 59.8, 31.9, 29.8 (2C), 29.7, 29.6 (3C), 29.3, 29.2, 29.1, 29.0, 28.5, 28.3, 26.5 (2C), 25.8, 22.7, 20.8, 20.2, 18.0, 15.3 (2C), 14.3, 14.1, −4.2 (2C); HREIMS [(M−OEt)$^+$]: calcd for $C_{29}H_{57}O_4Si$, 497.4026; found, 497.3991.

4.1.4. (2E,6R,7R)-6-(tert-Butyldimethylsilyloxy)-7-ethoxyethoxy-2-nonadecen-1-ol (**12**)

To a solution of **11** (2.32 g, 4.29 mmol) in CH_2Cl_2 (20 mL) was added DIBALH (1.68 mL, 9.43 mmol) at −78 °C. After being stirred for 15 min at the same temperature, the reaction was quenched with MeOH (5.0 mL). The mixture was warmed to room temperature, filtered through Celite and silica gel layer. The filtrate was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=10:1) to give **12** (2.08 g, 97%) as a colorless oil. IR (film): ν_{max}=3393, 2926, 2855, 1670, 1463, 1387, 1255, 1094, 969, 836, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=5.74–5.63 (2H, m), 4.73 (0.4H, q, J=6.3 Hz), 4.65 (0.6H, q, J=6.3 Hz), 4.09–4.07 (2H, m), 3.81–3.78 (0.6H, m), 3.70–3.66 (0.4H, m), 3.65–3.42 (2.4H, m), 3.38–3.35 (0.6H, m), 2.27–2.17 (1H, m), 2.01–1.94 (1H, m), 1.72–1.61 (2H, m), 1.50 (1H, br), 1.46–1.38 (2H, m), 1.35–1.20 (20H, m), 1.30 (1.8H, d, J=6.3 Hz), 1.28 (1.2H, d, J=6.3 Hz), 1.21 (1.8H, t, J=7.0 Hz), 1.20 (1.2H, t, J=7.0 Hz), 0.89 (9H, s), 0.88 (3H, t, J=7.0 Hz), 0.07 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=133.5, 133.3, 129.0, 128.9, 101.2, 98.9, 81.1, 78.3, 73.0, 72.3, 63.8 (2C), 60.6, 60.0, 31.9, 30.3, 30.1, 29.8 (2C), 29.7, 29.6 (4C), 29.3, 29.2, 29.0, 28.6, 28.4, 26.5, 25.8, 22.7, 20.8, 20.3, 18.0, 15.4, 15.3, 14.1, −4.2 (2C); HREIMS [(M−OEE)$^+$]: calcd for $C_{25}H_{51}O_2Si$, 411.3658; found, 411.3657.

4.1.5. (2E,6R,7R)-6-(tert-Butyldimethylsilyloxy)-7-ethoxyethoxy-nonadec-2-ene-3′-phenylbenzoate (**13**)

To a solution of **12** (2.08 g, 4.16 mmol) in pyridine (20 mL) were added 4-biphenyl-carbonyl chloride (1.35 g, 6.24 mmol) and DMAP (1.02 g, 8.52 mmol) at 0 °C. The mixture was stirred at room temperature for 15 h. The reaction was quenched with saturated aqueous NH_4Cl, and the solution was stirred for 3 h. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=20:1) to give **13** (2.71 g, 96%) as a colorless oil. IR (film): ν_{max}=3059, 3032, 2926, 2854, 1721, 1610, 1463, 1267, 1099, 970, 835, 775, 748, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=8.12 (2H, d, J=8.5 Hz), 7.66 (2H, d, J=8.5 Hz), 7.63 (2H, d, J=7.5 Hz), 7.47 (2H, t, J=7.5 Hz), 7.40 (1H, t, J=7.5 Hz), 5.92–5.85 (1H, m), 5.76–5.70 (1H, m), 4.78 (2H, d, J=6.0 Hz), 4.73 (0.4H, q, J=5.3 Hz), 4.66 (0.6H, q, J=5.3 Hz), 3.82–3.80 (0.6H, m), 3.71–3.69 (0.4H, m), 3.66–3.42 (2.4H, m), 3.39–3.36 (0.6H, m), 2.33–2.27 (1H, m), 2.07–1.99 (1H, m), 1.66–1.64 (2H, m), 1.48–1.43 (2H, m), 1.40–1.25 (20H, m), 1.31 (1.8H, d, J=5.8 Hz), 1.29 (1.2H, d, J=5.8 Hz), 1.20 (1.8H, t, J=7.0 Hz), 1.18 (1.2H, t, J=7.0 Hz), 0.91 (s, 9H), 0.88 (3H, t, J=7.0 Hz), 0.07 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=166.3, 145.6, 140.1, 136.6, 136.4, 130.1, 129.1, 128.9, 128.1, 127.3, 127.0, 124.0, 123.9, 101.1, 98.9, 81.0, 78.3, 73.1, 72.1, 65.8, 65.7, 60.6, 59.8, 31.9, 30.0, 29.8, 29.7 (2C), 29.6 (3C), 29.4, 29.3, 29.1, 28.5, 28.4, 26.6, 25.9, 22.7, 20.9, 20.3, 18.0, 15.4,

15.3, 14.1, −4.2, −4.5; HREIMS [(M−C_3H_7O)$^+$]: calcd for $C_{39}H_{61}O_4Si$, 621.4339; found, 621.4312.

4.1.6. (2E,6R,7R)-6-(tert-Butyldimethylsilyloxy)-7-hydroxy-2-nonadecenyl-3′-phenylbenzoate (**7**)

To a solution of **13** (2.71 g, 3.99 mmol) in THF/H_2O (1:1, 20 mL) was added a few drops of 0.5 N HCl. The mixture was stirred at room temperature for 21 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=15:1) to give **7** (2.06 g, 85%) as a colorless oil. $[\alpha]_D^{18}$ −0.73 (*c* 0.92, $CHCl_3$); IR (film): ν_{max}=3516, 3059, 3032, 2924, 2853, 1719, 1609, 1463, 1267, 1100, 970, 836, 776, 748, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.67–7.65 (3H, m), 7.64–7.61 (3H, m), 7.51–7.46 (2H, m), 7.42–7.38 (1H, m), 5.89–5.83 (1H, m), 5.74–5.69 (1H, m), 4.79 (2H, d, *J*=6.0 Hz), 3.57–3.54 (1H, m), 3.44 (1H, m), 2.19–2.06 (3H, m), 1.80–1.73 (1H, m), 1.59 (1H, br s), 1.58–1.51 (2H, m), 1.46–1.31 (3H, m), 1.35–1.20 (17H, m), 0.91 (9H, s), 0.88 (3H, t, *J*=7.0 Hz), 0.10 (3H, s), 0.09 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=166.1, 145.5, 139.9, 135.8, 130.1, 129.0, 128.8, 128.0, 127.2, 126.9, 124.5, 124.2, 81.6, 74.4, 72.6, 65.4, 33.8, 32.7, 31.8, 29.6 (2C), 29.6 (5C), 29.3, 27.9, 25.9, 25.8, 22.6, 18.0, 14.1, −4.2, −4.6; HRFABMS [(M−H_2O+H)$^+$]: calcd for $C_{38}H_{59}O_3Si$, 591.4233; found, 591.4212.

4.1.7. (2R,3R,6R)-3-(tert-Butyldimethylsilyloxy)-2-dodecyl-6-(1′-ethenyl)tetrahydropyran (**6a**)

To a solution of **7** (2.06 g, 3.39 mmol) in dry CH_2Cl_2 (15 mL) was added $(CH_3CN)_2PdCl_2$ (86.9 mg, 0.339 mmol) at −10 °C under an argon gas atmosphere, and the mixture was stirred at the same temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=50:1) to give the mixture of **6a** and **6b** (1.03 g, 74%) as a colorless oil. Further purification by PTLC (hexane/AcOEt=50:1) to give **6a** (953 mg, 69%). $[\alpha]_D^{20}$ +8.97 (*c* 1.00, $CHCl_3$); IR (film): ν_{max}=3080, 3014, 2925, 2854, 1648, 1464, 1253, 1087, 918, 835, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=5.91 (1H, ddd, *J*=17.3, 10.5, 6.0 Hz), 5.22 (1H, dt, *J*=17.3, 1.2 Hz), 5.08 (1H, dt, *J*=10.5, 1.1 Hz), 3.81 (1H, dd, *J*=10.5, 6.0 Hz), 3.61 (1H, m), 3.26 (1H, t, *J*=6.6 Hz), 1.88–1.85 (1H, m), 1.68–1.60 (4H, m), 1.41–1.30 (4H, m), 1.35–1.20 (17H, m), 0.91 (9H, s), 0.88 (3H, t, *J*=6.8 Hz), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=139.7, 114.7, 80.1, 78.5, 66.4, 32.3, 31.9, 31.7, 29.8, 29.7, 29.6 (2C), 29.4, 25.9, 25.8, 25.7 (2C), 22.7, 18.2, 14.1, −4.5, −4.7; HRCIMS [(M+H)$^+$]: calcd for $C_{25}H_{51}O_2Si$, 411.3658; found, 411.3661.

4.1.8. (2R,3R,6R,1′S)-3-(tert-Butyldimethylsilyloxy)-6-(1′,2′-dihydroxyethyl)-2-dodecyltetrahydropyran (**14**)

A suspension of AQN(DHQD)$_2$ (18.0 mg, 20.9 μmol), $K_2OsO_2(OH)_4$ (3.1 mg, 8.4 μmol), $K_3[Fe(CN)_6]$ (2.06 g, 6.27 mmol), and K_2CO_3 (867 mg, 6.27 mmol) in *t*-BuOH/H_2O (1:1, 10 mL) was stirred at 0 °C for 15 min. A solution of **6a** (856 mg, 2.09 mmol) in *t*-BuOH (3.0 mL) and $CH_3SO_2NH_2$ (199 mg, 2.09 mmol) was added to the suspension. The mixture was stirred 22 h at same temperature. The reaction was quenched with saturated aqueous Na_2SO_3 and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product showed 84% de by ^{1}H NMR analysis of the corresponding Mosher ester. The residue was purified by PTLC (hexane/AcOEt=3:1) to give **14** (834 mg, 90%) as a colorless oil. $[\alpha]_D^{21}$ +3.09 (*c* 1.40, $CHCl_3$); IR (film): ν_{max}=3389, 2925, 2854, 1464, 1376, 1253, 1097, 1027, 836, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=3.88 (1H, d, *J*=11.5 Hz), 3.70 (1H, m), 3.61 (1H, m), 3.60 (1H, m), 3.55 (1H, m), 3.22 (1H, dd, *J*=5.0, 4.5 Hz), 2.80 (1H, d, *J*=8.0 Hz), 2.62 (1H, d, *J*=7.5 Hz), 1.89 (1H, m), 1.81 (1H, m), 1.66–1.60 (2H, m), 1.66–1.54 (4H, m), 1.41–1.36 (2H, m), 1.35–1.20 (16H, m), 0.91 (9H, s), 0.88 (3H, t, *J*=6.8 Hz), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=80.4, 80.3, 73.0, 66.5, 63.7, 32.2, 31.9, 31.2 (2C), 29.7, 29.6 (2C), 29.3, 25.8 (2C), 25.6, 22.7, 21.5, 18.1, 14.1, −4.5, −4.9; HREIMS [(M−*t*Bu)$^+$]: calcd for $C_{21}H_{43}O_4Si$, 387.2931; found, 387.2924.

4.1.9. (2R,3R,6R,1′S)-3-(tert-Butyldimethylsilyloxy)-6-(2′-tert-butyldimethylsilyloxy-1′-hydroxyethyl)-2-dodecyltetrahydropyran (**15**)

To a solution of **14** (834 mg, 1.88 mmol), Et_3N (0.39 mL, 2.82 mmol) and DMAP (2.3 mg, 0.019 mmol) in CH_2Cl_2 (10 mL) was added TBSCl (312 mg, 2.07 mmol). The mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=20:1) to give **15** (1.02 g, 98%) as a colorless oil. $[\alpha]_D^{21}$ −3.57 (*c* 1.03, $CHCl_3$); IR (film): ν_{max}=3478, 2926, 2855, 1463, 1254, 1098, 836, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=3.74 (2H, d, *J*=4.5 Hz), 3.58 (1H, m), 3.54–3.53 (1H, m), 3.24–3.30 (1H, m), 3.20 (1H, dd, *J*=7.8, 3.8 Hz), 2.50 (1H, d, *J*=5.5 Hz), 1.90–1.87 (1H, m), 1.76–1.69 (1H, m), 1.55–1.62 (5H, m), 1.36–1.34 (2H, m), 1.40–1.25 (17H, m), 0.90 (18H, s), 0.88 (3H, t, *J*=7.0 Hz), 0.07 (6H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=80.1, 77.3, 73.7, 67.0, 63.4, 32.3, 31.9, 31.5, 29.7 (2C), 29.6 (2C), 29.4, 25.9, 25.8 (4C), 22.7, 21.7, 18.3, 18.2, 14.1, −4.5, −4.7, −5.4, −5.5; HREIMS [(M−Me)$^+$]: calcd for $C_{30}H_{63}O_4Si_2$, 543.4265; found, 543.4263.

4.1.10. (2R,3R,6R,1′R)-2-Dodecyl-6-(1′,2′-epoxyethyl)-tetrahydropyran-3-ol (**16**)

To a solution of **15** (1.02 g, 1.84 mmol) and Et_3N (0.51 mL, 3.68 mmol) in CH_2Cl_2 (10 mL) was added MsCl (0.17 mL, 2.21 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl, and whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in THF (5.0 mL), and then TBAF [1.0 M solution in THF (7.2 mL, 7.2 mmol)] was added to this solution at 0 °C. After the mixture was stirred for 12 h, the reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=20:1) to give **16** (488 mg, 85%) as a colorless oil. $[\alpha]_D^{22}$ +12.4 (*c* 1.06, $CHCl_3$); IR (film): ν_{max}=3451, 3046, 2924, 2853, 1466, 1084 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=3.61 (1H, m), 3.33 (1H, t, *J*=7.0 Hz), 3.28 (1H, ddd, *J*=11.5, 4.5, 2.5 Hz), 3.01 (1H, dd, *J*=7.3, 4.8 Hz), 2.78 (1H, m), 2.69 (1H, dd, *J*=5.0, 3.0 Hz), 2.03 (2H, m), 1.78 (2H, m), 1.70–1.60 (2H, m), 1.53–1.40 (2H, m), 1.40–1.20 (19H, m), 0.88 (3H, t, *J*=7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=80.1, 78.0, 65.8, 54.0, 43.8, 31.9, 31.6, 30.5, 29.6 (2C), 29.5 (2C), 29.3, 25.5, 22.7, 21.9, 14.1; HRFABMS [(M+H)$^+$]: calcd for $C_{19}H_{37}O_3$, 313.2743; found, 313.2741.

4.1.11. (2R,3R,6R,1′R)-2-Dodecyl-6-(1′-hydroxy-3′-butyn-1′-yl)-tetrahydropyran-3-ol (**17**)

To a suspension of lithium acetylide, an ethylenediamine complex (1.44 g, 15.6 mmol) in DMSO (15 mL) was added **16** (488 mg, 1.56 mmol) in DMSO (5.0 mL) at 0 °C. The reaction mixture was stirred for 18 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=20:1) to give **17** (442 mg, 84%) as a colorless oil. $[\alpha]_D^{21}$ −16.1 (*c* 1.00, $CHCl_3$); IR (film): ν_{max}=3380, 3313, 2924, 2853, 2119, 1465, 1089 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=3.62 (2H, m), 3.47

(1H, m), 3.38 (1H, m), 2.68 (1H, br s), 2.52 (1H, ddd, J=17.0, 6.0, 2.5 Hz), 2.43 (1H, ddd, J=17.0, 6.0, 2.5 Hz), 2.17 (1H, br s), 2.02 (1H, t, J=2.5 Hz), 2.04 (1H, m), 1.77–1.70 (2H, m), 1.68–1.62 (2H, m), 1.52–1.46 (2H, m), 1.40–1.20 (20H, m), 0.88 (3H, t, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=80.5, 80.2, 79.2, 72.2, 70.2, 66.1, 31.9, 31.6, 30.5, 29.7, 29.6 (3C), 29.3, 25.6, 23.8, 23.0, 22.7, 21.5, 14.1; HRFABMS [(M+Na)$^+$]: calcd for $C_{21}H_{38}O_3Na$, 361.2719; found, 361.2720.

4.1.12. (2R,3R,6R,1′R)-2-Dodecyl-3-methoxymethoxy-6-(1′-methoxymethoxy-3′-butyn-1′-yl)tetrahydropyran (**4**)

To a solution of **17** (442 mg, 1.31 mmol) in dry CH_2Cl_2 (5.0 mL) were added *i*-Pr_2NEt (0.69 mL, 3.93 mmol) and MOMBr (0.26 mL, 3.14 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=5:1) to give **4** (430 mg, 77%) as a colorless oil. $[\alpha]_D^{19}$ −32.5 (*c* 1.08, $CHCl_3$); IR (film): ν_{max}=3312, 2925, 2853, 2120, 1467, 1151, 1103, 1038, 918 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=4.77 (1H, d, J=7.0 Hz), 4.76 (1H, d, J=7.0 Hz), 4.75 (1H, d, J=7.0 Hz), 4.61 (1H, d, J=7.0 Hz), 3.69 (1H, m), 3.62 (1H, ddd, J=11.5, 5.0, 1.5 Hz), 3.53 (1H, m), 3.40 (3H, s), 3.39 (3H, s), 3.34 (1H, m), 2.66 (1H, ddd, J=17.0, 6.3, 2.5 Hz), 2.43 (1H, ddd, J=17.0, 5.0, 2.5 Hz), 2.13 (1H, m), 1.96 (1H, t, J=2.5 Hz), 1.83–1.73 (2H, m), 1.62–1.59 (1H, m), 1.48–1.39 (3H, m), 1.40–1.25 (19H, m), 0.88 (3H, t, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=96.7, 95.2, 81.1, 80.2, 78.9, 77.5, 71.2, 69.6, 55.7 (2C), 31.9, 31.8, 29.6 (3C), 29.3, 27.8, 25.6, 22.8, 21.8, 21.0, 14.1; HRFABMS [(M+Na)$^+$]: calcd for $C_{25}H_{47}O_5$, 427.3423; found, 427.3424.

4.1.13. (5S,2′R,8′RS)-3-(2′-tert-Butyldimethylsilyloxy-8′-epoxynonan-1′-yl)-5-methyl-3,4-dihydrofuran-2-one (**19**)

To a solution of **18** (98.8 mg, 0.281 mmol) in CH_2Cl_2 (2.0 mL) were added *m*CPBA (149 mg, 0.562 mmol) and $NaHCO_3$ (155 mg, 1.85 mmol) at 0 °C. The reaction mixture was stirred at same temperature for 17 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=7:1) to give **19** (89.9 mg, 87%) as a colorless oil. IR (film): ν_{max}=3046, 2931, 2857, 1756, 1075, 836, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.11 (1H, d, J=1.0 Hz), 5.01 (1H, qd, J=7.0, 1.0 Hz), 3.98–3.94 (1H, m), 2.91–2.88 (1H, m), 2.74 (1H, dd, J=4.8, 4.3 Hz), 2.46 (1H, dd, J=5.0, 2.5 Hz), 2.43 (3H, dd, J=4.3, 1.3 Hz), 1.58–1.50 (2H, m), 1.49–1.44 (5H, m), 1.41 (3H, d, J=7.0 Hz), 1.35 (2H, m), 0.88 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=174.0, 151.5, 130.8, 77.4, 70.1, 52.3, 47.0, 36.8, 32.7, 32.4, 29.5, 25.9, 25.1, 25.0, 19.0, 18.0, −4.5.

4.1.14. (5S,2′R,8′R)-3-(2′-tert-Butyldimethylsilyloxy-8′-epoxynonan-1′-yl)-5-methyl-3,4-dihydrofuran-2-one (**5**)

To a solution of **19** (89.9 mg, 0.244 mmol) and AcOH (0.28 μL, 4.88 μmol) in THF (20 μL) were added (*R*,*R*)-(salen)-Co^{III} (0.7 mg, 1.22 μmol) and H_2O (2.0 μL) at 0 °C. The mixture was stirred at room temperature for 24 h. The mixture was concentrated and purified by PTLC (hexane/AcOEt=5:1) to give **5** (38.6 mg, 43%) as a colorless oil. $[\alpha]_D^{20}$ +22.2 (*c* 1.02, $CHCl_3$); IR (film): ν_{max}=3045, 2930, 2856, 1755, 1076, 836, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.12 (1H, d, J=1.0 Hz), 5.01 (1H, qd, J=6.8, 1.0 Hz), 3.98–3.94 (1H, m), 2.91 (1H, m), 2.74 (1H, dd, J=4.8, 4.3 Hz), 2.46 (1H, dd, J=5.0, 2.8 Hz), 2.43 (3H, dd, J=4.3, 1.3 Hz), 1.54–1.50 (2H, m), 1.46–1.43 (5H, m), 1.41 (3H, d, J=7.0 Hz), 1.35–1.34 (2H, m), 0.88 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=174.0, 151.5, 130.9, 77.4, 70.2, 52.3, 47.1, 36.8, 32.8, 32.4, 29.5, 25.9 (3C), 25.1, 19.0, 18.1, −4.4 (2C); HRFABMS [(M+H)$^+$]: calcd for $C_{20}H_{37}O_4Si$, 369.2461; found, 369.2455.

4.1.15. (2R,3R,6R,1′R,6′R,12′R,5″S)-6-(12′-tert-Butyldimethylsilyloxy-6′-hydroxy-1′-methoxymethoxy-13′-[5″-methyl-3″,4″-dihydrofuran-2″-on-3″-yl]-tridec-3′-ynyl)-2-dodecyl-3-methoxymethoxytetrahydropyran (**20**)

To a solution of **6a** (224 mg, 0.525 mmol) in dry THF (5.0 mL) was added *n*-BuLi [1.56 M solution in hexane (0.30 mL, 0.473 mmol)] at −78 °C under an argon gas atmosphere. After being stirred for 1 h at the same temperature, $BF_3\cdot Et_2O$ (0.13 mL, 0.420 mmol) was added and the mixture was stirred for 30 min at −78 °C. To the resultant mixture was added **5** (38.6 mg, 0.105 mmol) in dry THF (1.0 mL) and stirred for 2 h at −78 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/EtOAc=3:1) to give **20** (62.8 mg, 75%) as a colorless oil. $[\alpha]_D^{21}$ −15 (*c* 0.72, $CHCl_3$); IR (film): ν_{max}=3477, 2926, 2854, 2120, 1757, 1463, 1150, 1099, 1033, 836, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.12 (1H, s), 5.00 (1H, q, J=6.8 Hz), 4.83–4.74 (3H, m), 4.61 (1H, d, J=7.0 Hz), 3.97–3.93 (1H, m), 3.68–3.66 (2H, m), 3.57–3.52 (2H, m), 3.39 (3H, s), 3.38 (3H, s), 3.32 (1H, m), 2.63–2.59 (1H, m), 2.43–2.34 (5H, m), 2.25 (1H, dd, J=16.5, 7.0 Hz), 2.14–2.12 (1H, m), 1.74–1.82 (2H, m), 1.59–1.52 (1H, m), 1.49–1.45 (10H, m), 1.41 (3H, d, J=6.8 Hz), 1.40–1.26 (22H, m), 0.88 (3H, t, J=6.8 Hz), 0.87 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=174.0, 151.5, 130.8, 96.6, 95.2, 80.3, 79.7, 79.4, 78.1, 77.8, 77.4, 71.1, 70.2, 70.1 (2C), 55.7, 55.6, 36.9, 36.3, 32.7, 31.9, 31.8, 29.7 (3C), 29.6, 29.3, 27.9 (2C), 27.8, 25.9, 25.1 (3C), 22.7, 21.8, 21.3, 19.0, 18.0, 14.1, −4.5; HRFABMS [(M+Na)$^+$]: calcd for $C_{45}H_{82}O_9SiNa$, 817.5626; found, 817.5630.

4.1.16. Pyranicin (**1**)

To a solution of **20** (62.8 mg, 0.0789 mmol) in 1,2-diethoxyethane (1.0 mL) was added *p*-TsHNNH$_2$ (1.03 g, 5.52 mmol), and the resulting mixture was stirred for 0.5 h at 120 °C. A solution of AcONa (550 mg, 6.71 mmol) in H_2O (1.0 mL) was added dropwise to a solution and stirred at same temperature for 4 h. The reaction was quenched with H_2O and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in dimethyl sulfide (1.0 mL) and a few drops of $BF_3\cdot Et_2O$ was added at 0 °C. After being stirred for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=1:5) to give pyranicin (**1**) (41 mg, 87%) as a colorless wax. $[\alpha]_D^{19}$ +17 (*c* 0.41, $CHCl_3$); IR (film): ν_{max}=3392, 2925, 2853, 1741, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.19 (1H, d, J=1.0 Hz), 5.07 (1H, qd, J=6.7, 1.0 Hz), 3.85 (1H, m), 3.61 (3H, m), 3.46 (1H, m), 3.34 (1H, dd, J=7.5, 6.0 Hz), 3.19 (1H, ddd, J=11.0, 7.0, 2.0 Hz), 2.76 (1H, br s), 2.52 (1H, dt, J=15.2, 1.6 Hz), 2.45 (1H, br s), 2.40 (1H, dd, J=15.3, 8.3 Hz), 2.02–1.99 (2H, m), 1.70 (1H, br s), 1.70–1.50 (3H, m), 1.48–1.46 (6H, m), 1.43 (3H, d, J=6.5 Hz), 1.42–1.26 (33H, m), 0.88 (3H, t, J=6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=174.6, 151.9, 131.1, 81.2, 80.0, 78.0, 74.0, 71.8, 69.9, 66.1, 37.3, 33.4, 32.3, 31.9, 31.6, 30.5, 29.7, 29.6 (4C), 29.5, 29.3, 25.6 (2C), 25.5, 25.4, 25.3, 22.7, 21.6, 19.1, 14.1; HRFABMS [(M+H)$^+$]: calcd for $C_{35}H_{65}O_7$, 597.4730; found, 597.4745.

4.1.17. (5′EZ,2R,3R,6R,1′R,12′R,5″S)-6-(12′-tert-Butyldimethylsilyloxy-1′-methoxymethoxy-13′-[5″-methyl-3″,4″-dihydrofuran-2″-on-3″-yl]tridec-5′-en-3′-ynyl)-3-methoxymethoxytetrahydropyran (**22**)

To a solution of **21** (70 mg, 0.146 mmol) in benzene (1.0 mL) were added Et_3N (0.05 mL, 0.29 mmol) and $Cl_2Pd(PPh_3)_2$ (10.3 mg, 14.5 μmol). After the mixture had been stirred for 30 min, the solution of **6a** (62 mg, 0.146 mmol) and CuI (5.5 mg, 0.029 mmol) were added and the resulting mixture was stirred for 19 h. The

reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the whole was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=1:5) to give **22** (57 mg, 51%) as a colorless oil. IR (film): ν_{max}=2926, 2854, 2214, 1758, 1464, 1150, 1036, 919, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=7.13 (1H, d, J=1.0 Hz), 6.03 (0.9H, dt, J=15.8, 7.1 Hz), 5.82 (0.2H, m), 5.43 (0.9H, d, J=15.8 Hz), 5.01 (1H, qd, J=6.3, 1.0 Hz), 4.77 (1H, d, J=6.5 Hz), 4.76 (2H, s), 4.61 (1H, d, J=7.0 Hz), 3.95 (1H, m), 3.68 (1H, m), 3.59 (1H, ddd, J=11.5, 4.9, 1.6 Hz), 3.53 (1H, m), 3.40 (3H, s), 3.39 (3H, s), 3.35 (1H, m), 2.80–2.75 (1H, m), 2.60–2.50 (1H, m), 2.42 (2H, m), 2.12 (1H, m), 2.07 (2H, m), 1.83–1.72 (2H, m), 1.69 (1H, m), 1.62–1.54 (1H, m), 1.48–1.25 (34H, m), 1.41 (3H, d, J=6.3 Hz), 0.88 (3H, t, J=7.0 Hz), 0.87 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=174.0, 151.8, 151.5, 143.6, 142.8, 130.8, 109.8, 109.3, 95.5, 95.0, 84.9, 80.4, 80.3, 80.2, 77.7, 77.5, 71.1, 70.1, 69.8, 55.7, 36.8, 32.9, 32.7, 31.9, 31.7, 29.7, 29.6 (2C), 29.3, 29.2, 28.7, 27.6, 25.8 (2C), 25.6, 24.9, 22.7, 21.9, 21.8, 19.0, 18.0, 14.0, −4.5 (2C); HRFABMS [$(M+H)^+$]: calcd for $C_{45}H_{79}O_8Si$, 775.5544; found, 775.5533.

4.1.18. *(2R,3R,6R,1′R,12′R,5″S)-6-(12′-tert-Butyldimethylsilyloxy-1′-methoxymethoxy-13′-[5″-methyl-3″,4″-dihydrofuran-2″-on-3″-yl]tridecyl-2-dodecyl)-3-methoxymethoxytetrahydropyran (**23**)*

To a solution of **22** (38 mg, 0.049 mmol) in 1,2-diethoxyethane (1.0 mL) was added *p*-$TsHNNH_2$ (672 mg, 3.43 mmol), and the resulting mixture was stirred for 0.5 h at 120 °C. A solution of AcONa (341 mg, 4.16 mmol) in H_2O (1.0 mL) was added dropwise to a solution and stirred at same temperature for 4 h. The reaction was quenched with H_2O and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=1:3) to give **23** (26 mg, 68%) as a colorless oil. $[\alpha]_D^{19}$ +9.1 (*c* 0.26, $CHCl_3$); IR (film): ν_{max}=2925, 2854, 1760, 1465, 1373, 1318, 1254, 1210, 1150, 1100, 1035, 919, 837, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=7.13 (1H, d, J=1.0 Hz), 5.01 (1H, qd, J=6.6, 1.0 Hz), 4.81 (1H, d, J=6.5 Hz), 4.77 (1H, J=7.0 Hz), 4.70 (1H, J=6.5 Hz), 4.62 (1H, J=7.0 Hz), 3.94 (1H, m), 3.52 (2H, m), 3.38 (1H, m), 3.38 (6H, s), 3.32 (1H, m), 2.42 (2H, dd, J=8.0, 5.5 Hz), 2.12 (1H, m), 1.76–1.51 (6H, m), 1.47–1.25 (43H, m), 1.41 (3H, d, J=6.6 Hz), 0.88 (3H, t, J=6.8 Hz), 0.87 (9H, s), 0.05 (3H, s), 0.02 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=174.0, 151.5, 130.8, 97.0, 95.1, 80.7, 80.0, 79.8, 77.5, 71.1, 70.2, 55.7, 37.0, 32.7, 31.9, 31.8, 30.6, 29.8, 29.7 (2C), 29.6 (3C), 29.3, 27.8, 25.9, 25.8, 25.7, 25.2, 25.1, 22.7, 22.0, 19.0, 18.0, 14.1, −4.5 (2C); HRFABMS [$(M+H)^+$]: calcd for $C_{45}H_{85}O_8Si$, 781.6014; found, 781.6019.

4.1.19. *10-Deoxypyranicin (**2**)*

To a solution of compound **23** (24 mg, 0.031 mmol) in dimethyl sulfide (1.0 mL) was added a few drops of $BF_3\cdot Et_2O$ at 0 °C. After being stirred for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=1:2) to give **2** (13 mg, 74%) as a colorless solid. Mp 36–37 °C; $[\alpha]_D^{19}$ +12 (*c* 0.20, $CHCl_3$); IR (film): ν_{max}=3413, 2924, 2853, 1741, 1465, 1085, 1028, 849, 721 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=7.19 (1H, d, J=1.0 Hz), 5.07 (1H, qd, J=6.8, 1.0 Hz), 3.85 (1H, m), 3.61 (1H, m), 3.45 (1H, m), 3.34 (1H, dd, J=7.8, 5.8 Hz), 3.20 (1H, ddd, J=11.3, 7.0, 2.3 Hz), 2.53 (1H, dt, J=15.3, 1.6 Hz), 2.40 (1H, dd, J=15.3, 8.3 Hz), 2.00 (2H, m), 1.71–1.25 (44H, m), 1.43 (3H, d, J=6.8 Hz), 0.88 (3H, t, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=174.6, 151.8, 131.2, 81.2, 80.0, 78.0, 74.0, 70.0, 66.2, 37.4, 33.3, 32.4, 31.9, 31.6, 30.6, 29.7, 29.6 (4C), 29.5, 29.3, 25.6 (2C), 25.3, 22.7, 21.6, 19.1, 14.1; HRFABMS [$(M+H)^+$]: calcd for $C_{35}H_{65}O_6$, 581.4781; found, 581.4787.

4.1.20. *(5′E,2R,3R,6R,1′R,5″S)-2-Dodecyl-3-methoxymethoxy-6-(1′-methoxymethoxy-13′-[5″-methyl-3″,4″-dihydrofuran-2″-on-3″-yl]tridec-5′-en-3′-ynyl)tetrahydropyran (**25**)*

To a solution of **24** (30 mg, 0.086 mmol) in benzene (1.0 mL) were added Et_3N (0.024 mL, 0.17 mmol) and $Cl_2Pd(PPh_3)_2$ (6.1 mg, 8.6 μmol). After the mixture had been stirred for 30 min, the solution of **4** (37 mg, 0.087 mmol) and CuI (3.3 mg, 0.017 mmol) was added and the resulting mixture was stirred for 19 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the whole was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=1:5) to give **25** (37 mg, 67%) as a colorless oil. IR (film): ν_{max}=2925, 2853, 2219, 1758, 1465, 1372, 1318, 1212, 1150, 1102, 1035, 955, 918, 722 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=6.99 (1H, d, J=1.5 Hz), 6.04 (1H, dt, J=15.5, 7.3 Hz), 5.43 (1H, d, J=15.5 Hz), 5.00 (1H, qd, J=6.8, 1.5 Hz), 4.77 (1H, d, J=6.5 Hz), 4.76 (2H, s), 4.61 (1H, d, J=6.5 Hz), 3.68 (1H, m), 3.59 (1H, ddd, J=11.5, 4.9, 1.6 Hz), 3.53 (1H, m), 3.40 (3H, s), 3.39 (3H, s), 3.34 (1H, m), 2.74 (1H, ddd, J=17.0, 6.3, 1.8 Hz), 2.53 (1H, ddd, J=17.0, 5.4, 1.6 Hz), 2.26 (2H, t, J=7.0 Hz), 2.13 (1H, m), 2.07 (2H, m), 1.83–1.72 (2H, m), 1.62–1.60 (2H, m), 1.57–1.51 (2H, m), 1.50–1.25 (34H, m), 1.41 (3H, d, J=6.8 Hz), 0.88 (3H, t, J=6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=173.9, 148.9, 143.6, 134.3, 109.8, 96.6, 95.1, 84.9, 80.4, 80.2, 79.2, 77.8, 77.4, 71.1, 55.7, 32.9, 31.9, 31.8, 29.7, 29.6 (2C), 29.4, 29.3, 29.1, 29.0, 28.7, 27.8, 27.4, 25.6, 25.2, 22.7, 21.9, 21.8, 19.2, 14.1; HRFABMS [$(M+H)^+$]: calcd for $C_{39}H_{67}O_7$, 647.4886; found, 647.4890.

4.1.21. *4,10-Dideoxypyranicin (**3**)*

To a solution of **25** (25.0 mg, 0.039 mmol) in 1,2-diethoxyethane (1.0 mL) was added *p*-$TsHNNH_2$ (531 mg, 2.71 mmol), and the resulting mixture was stirred for 0.5 h at 120 °C. A solution of AcONa (270 mg, 3.29 mmol) in H_2O (1.0 mL) was added dropwise to a solution and stirred at same temperature for 4 h. The reaction was quenched with H_2O and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in dimethyl sulfide (1.0 mL) and a few drops of $BF_3\cdot Et_2O$ was added at 0 °C. After being stirred for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (hexane/AcOEt=1:5) to give **3** (8 mg, 37%, 2 steps) as a colorless wax. Mp 61–63 °C; $[\alpha]_D^{18}$ +12.5 (*c* 0.40, $CHCl_3$); IR (film): ν_{max}=3398, 2919, 2850, 1754, 1467, 1375, 1319, 1200, 1086, 1028, 874, 721 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=6.99 (1H, d, J=1.5 Hz), 5.00 (1H, qd, J=6.8, 1.5 Hz), 3.61 (1H, m), 3.45 (1H, m), 3.34 (1H, dd, J=7.8, 5.8 Hz), 3.19 (1H, ddd, J=11.0, 7.8, 2.5 Hz), 2.66 (1H, br s), 2.26 (2H, dt, J=7.8 Hz), 2.00 (1H, m), 1.82 (1H, d, J=8.0 Hz), 1.70–1.25 (47H, m), 1.41 (3H, d, J=6.8 Hz), 0.88 (3H, t, J=6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=173.9, 148.9, 134.3, 81.3, 80.0, 77.4, 74.1, 66.2, 32.4, 31.9, 31.6, 30.6, 29.7 (2C), 29.6 (2C), 29.5, 29.4, 29.3, 29.2, 27.4, 25.6, 25.3, 25.2, 22.7, 21.6, 19.2, 14.1; HRFABMS [$(M+H)^+$]: calcd for $C_{35}H_{65}O_5$, 565.4832; found, 565.4820.

4.2. Biochemical methods

Bovine heart submitochondrial particles were prepared by the method of Matsuno-Yagi and Hatefi,[26] and stored in a buffer containing 0.25 M sucrose and 10 mM Tris–HCl (pH 7.4) at −82 °C. The NADH oxidase activity in the particles was followed spectrometrically with a Shimadzu UV-3000 (340 nm, ε=6.2 $mM^{-1}\,cm^{-1}$) at 30 °C. The reaction medium (2.5 mL) contained 0.25 M sucrose, 1 mM $MgCl_2$, and 50 mM phosphate buffer (pH 7.4). The final mitochondrial protein concentration was 30 μg of protein/mL. The reaction was started by adding 50 μM NADH after the equilibration

of particles with inhibitor for 5 min. The IC_{50} values were averaged from three independent experiments.

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