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Bioorganic & Medicinal Chemistry 14 (2006) 3119–3130
Bioorganic & Medicinal Chemistry

Synthesis of (4*R*,15*R*,16*R*,21*S*)- and (4*R*,15*S*,16*S*,21*S*)-rollicosin, squamostolide, and their inhibitory action with bovine heart mitochondrial complex I

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Received 8 December 2005; revised 14 December 2005; accepted 15 December 2005
Available online 23 January 2006

Abstract—A convergent stereoselective synthesis of (4*R*,15*R*,16*R*,21*S*)- and (4*R*,15*S*,16*S*,21*S*)-rollicosin and squamostolide was accomplished via a Pd-catalyzed cross-coupling reaction. The inhibitory activity of these compounds was examined with bovine heart mitochondrial NADH-ubiquinone oxidoreductase. These compounds showed a remarkably weak inhibitory activity compared to ordinary acetogenins such as bullatacin. Our results indicate that to maintain potent inhibitory effect, the hydroxylated lactone cannot substitute for the hydroxylated mono- or bis-THF rings with a long alkyl chain that can be seen in ordinary acetogenins.

1. Introduction

Annonaceous acetogenins, that have been isolated from a number of tropical or subtropical plants of the *Annonaceae*, have attracted much attention due to a wide variety of biological activities, for example, cytotoxic, antitumoral, antimalarial, antibiotic, antiparastic, and antifeedant. More than 400 compounds have been isolated in the past two decades.[1] Most of them possess one or more tetrahydrofuran (THF) rings, together with an α,β-unsaturated γ-lactone part on a C-35 or C-37 carbon chain. Rollicosin (**1**) was isolated from *Rollinia mucosa* by Wu and co-workers.[2] Squamostolide (**3**) was isolated from *Annona squamosa* by Wei and co-workers.[3] These compounds possess a partial skeleton of ordinary annonaceous acetogenins containing two γ-lactone moieties on both sides of an aliphatic chain. Rollicosin may be generated from oxidative degradation of ordinary acetogenins such as murisolin (**4**)[4] and/or *cis*-murisolin (**5**)[5] and squamostolide from solamin (**6**)[6] and/or *cis*-solamin (**7**).[7] Moreover, these compounds may help to investigate the role of the terminal hydroxylated lactone moiety for its bioactivity instead of the hydroxylated THF moiety with long aliphatic chain that can be seen in the classical ordinary acetogenins. The absolute stereochemistry of rollicosin was reported to be (4*R*,15*R*,16*R*,21*S*). The absolute chemistry at C-4 and C-21 position was assigned in the *R* and *S* by the CD spectrum and the configurations of the C-15 and C-16 position of rollicosin were determined by comparison of optical rotation between rollicosin and (−)-muricatacin (**8**).[8] The absolute stereochemistry of squamostolide was also determined to be (15*R*,16*R*,21*S*) (Fig. 1).[3] Recently, synthesis of **1** was reported by Quinn and co-workers, and us, independently.[9a,b] The synthesis of the both of the enantiomers of **3** was also reported by Wu and co-workers.[10a,b] In this paper, we wish to report the synthesis of (4*R*,15*R*,16*R*,21*S*)-rollicosin (**1**), (4*R*,15*S*,16*S*,21*S*)-rollicosin (**2**), squamostolide (**3**), and their inhibitory activity with bovine heart

Keywords: Annonaceous acetogenin; Antitumor; Mitochondrial complex I; Stereoselective synthesis.
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doi:10.1016/j.bmc.2005.12.015

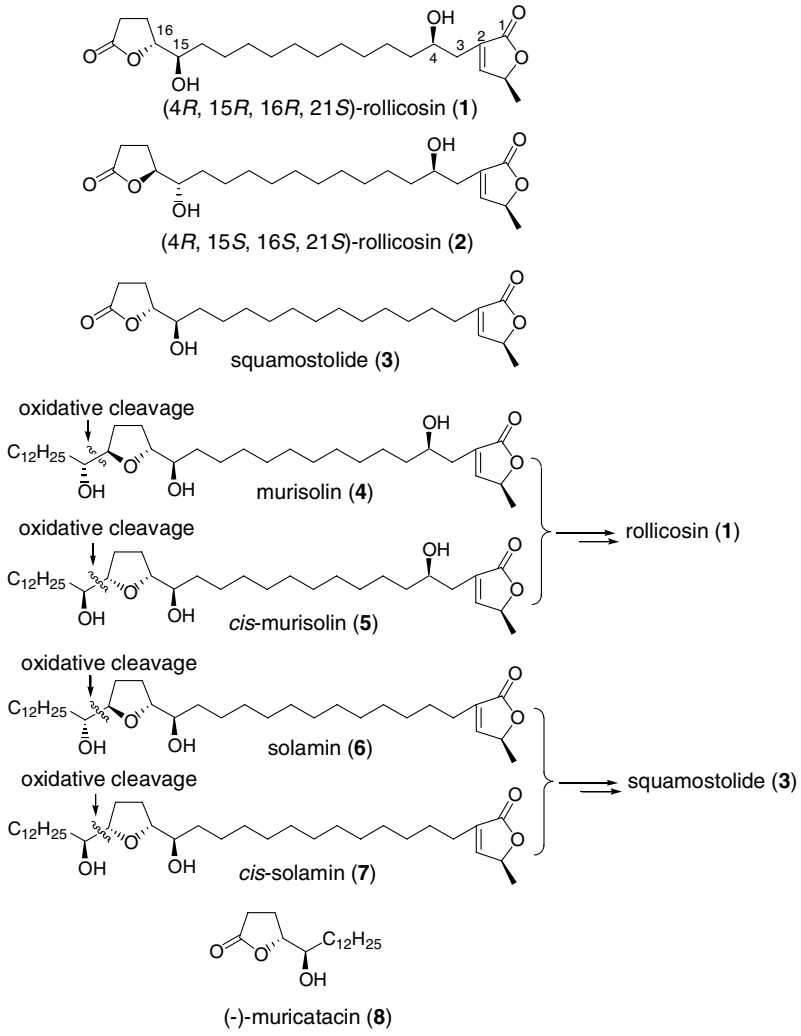


Figure 1. The structure of rollicosin and squamostolide.

mitochondrial NADH-ubiquinone oxidoreductase (complex I).

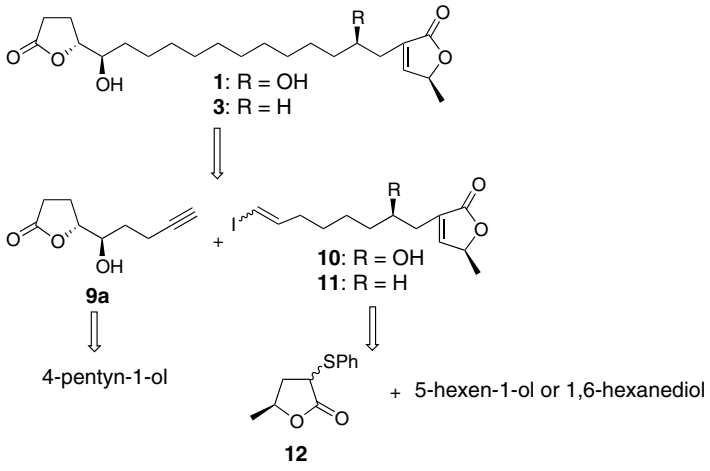
2. Results and discussion

2.1. Synthesis

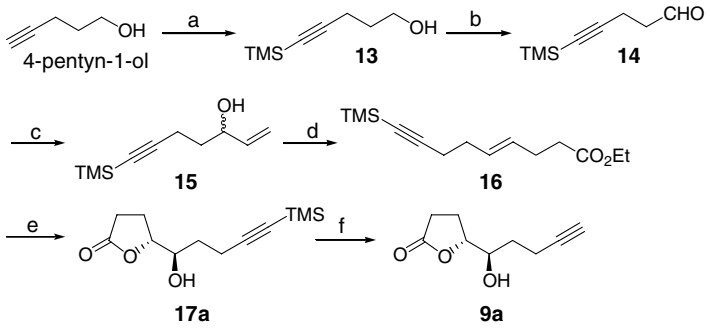
Scheme 1 outlines our synthetic strategy. The target compounds **1**, **2**, and **3** could be derived from hydroxy lactone **9a** and the α,β-unsaturated lactone **10** or **11**. The hydroxy lactone **9a** could be synthesized from 4-pentyn-1-ol by application of Wu and co-workers.[10a] Synthesis of **10** and **11** could be accomplished by use of 5-hexen-1-ol and/or 1,6-hexanediol, respectively. The known γ-lactone **12** could be prepared by J. D. White's method (Scheme 1).[11]

As shown in Scheme 2, the hydroxy lactone **9a** was constructed via a six-step process using M.-J. Wu's method with modification.[10a] The synthesis was started from 4-pentyn-1-ol, which was treated with trimethylsilyl chloride to afford alcohol **13**. Compound **13** was oxidized with SO_3·pyridine to give aldehyde **14**, which was reacted with vinylmagnesium chloride to afford allylic alcohol **15**. Johnson–Claisen rearrangement of **15** with triethyl orthoacetate and a catalytic amount of propionic acid gave **16**, followed by Sharpless asymmetric dihydroxylation using AD mix β[12] to furnish lactone **17**, which showed a 98% ee by a ^{1}H NMR analysis of the corresponding Mosher ester derivative. Removal of TMS group of **17** with TBAF gave the hydroxy lactone **9a** (Scheme 2).

The α,β-unsaturated lactone **10** was prepared as shown in Scheme 3. 5-Hexen-1-ol was treated with TBSCl and imidazole in DMF afforded the silyl ether **18**. Sharpless asymmetric dihydroxylation of **18** using $(DHQD)_2AQN$ as a ligand[13] gave diol **19**, which showed 93% ee based on a ^{1}H NMR analysis of the corresponding Mosher ester derivative. The 1,2-diol of **19** was protected as an acetonide with dimethoxypropane in the presence of *p*-TsOH to furnish **20**. Deprotection of the TBS group with TBAF gave **21**.[14] Compound **21** was transformed into iodide **22** via mesylation followed by iodination.[14] Alkylation of **22** with lithium acetylide ethylenediamine complex gave terminal acetylene **23**. Compound **23** was treated with *n*-Bu_3SnH and subse-



Scheme 1. Synthetic strategy of **1** and **3**.



Scheme 2. Synthesis of hydroxy lactone **9a**. Reagents and conditions: (a) i—*n*-BuLi, THF, 0 °C; ii—TMSCl, 0 °C to rt (71%); (b) SO_3·pyridine (96%); (c) vinylmagnesium chloride, THF, 0 °C (98%); (d) $CH_3C(OEt)_3$, propionic acid, 150 °C (64%); (e) AD mix β, $CH_3SO_2NH_2$, *t*-BuOH/H_2O, 0 °C (94%); (f) TBAF, THF, 0 °C (95%).

quently iodine to afford an *EZ* mixture (*E*/*Z* = 3/1) of vinyl iodide **24**. Deprotection of the acetonide group of **24** with methanolic HCl gave diol **25**. Selective sulfonylation of the primary hydroxyl group in **25** with triisopropylbenzenesulfonyl chloride in pyridine afforded the sulfonate **26**, which was then treated with NaH in THF to give epoxide **27**. Iodination of **27** with LiI gave hydroxyl iodide **28**, protection of the alcohol with TBSCl gave **29**.[15] The lactone **30** was obtained in 16% yield by alkylation of the enolate prepared by mixing **12**[11] and LDA with **29**. Unreacted **12** and **29** were recovered in 70% and 71% yield, respectively. These compounds could be used for the same reaction again. The α,β-unsaturated lactone **10** was obtained after oxidation of **30** with *m*CPBA followed by thermal elimination of sulfoxide under reflux in toluene (Scheme 3).

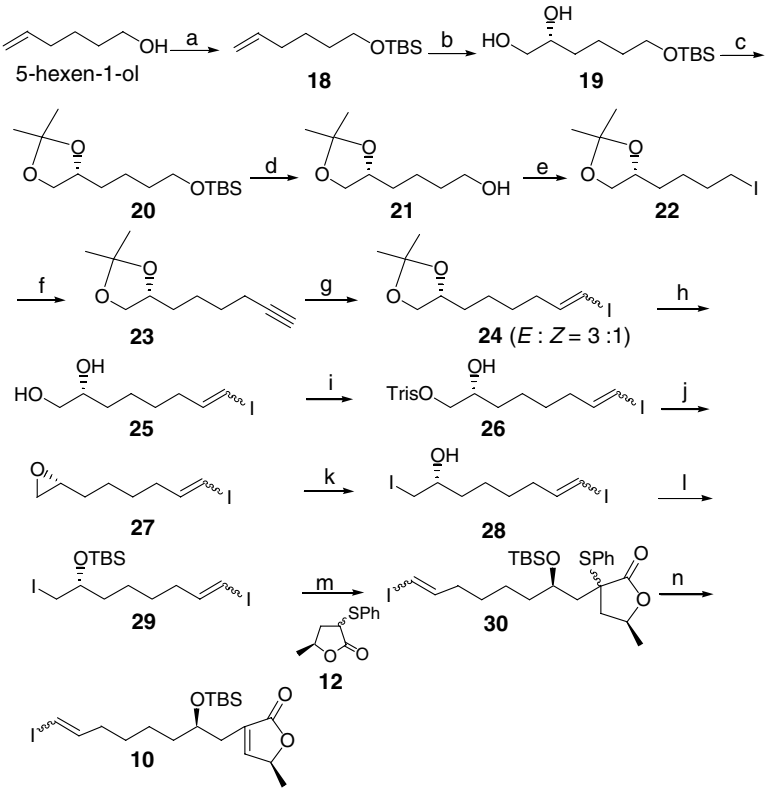
The segments **9a** and **10** were coupled by the Sonogashira cross-coupling reaction[16] to furnish cross-coupled product **31a** in 64% yield. Diimide reduction with *p*-$TsNHNH_2$ and NaOAc in ethylene glycol diethyl ether under reflux afforded saturated product **32a**.[17] Finally, deprotection of TBS ethers with HF and recrystallization from hexane afforded optically pure **1** (Scheme 4).

The ^1H NMR and ^{13}C NMR spectra of the synthetic **1** were in good agreement with those of natural rollicosin kindly provided by Prof. Y.-C. Wu.[18] The specific rotation of synthetic **1** showed different value compared to that of reported ($[\alpha]_D^{24}$ +2.5, *c* 0.29, ($CHCl_3$)). The $[\alpha]_D^{24}$ value of natural rollicosin was reported to be −26.0 (*c* 0.05, $CHCl_3$).[19] Therefore, we also prepared (4*R*,15*S*,16*S*,21*S*)-rollicosin (**2**), which has 15,16-*threo* relative stereochemistry like **1**,[20] starting from **9b** using the same procedure as that employed for **1** (Scheme 5).

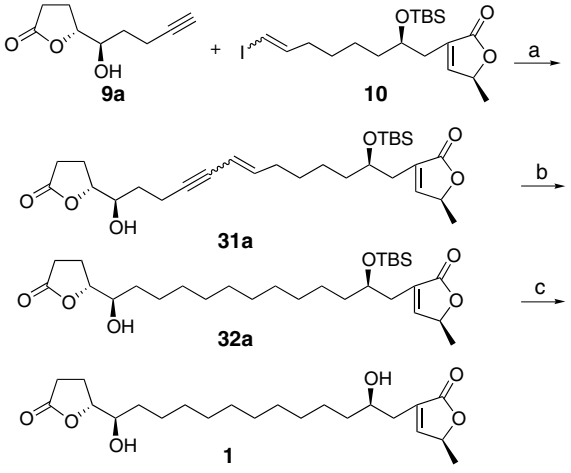
The specific rotation of **2** showed sharp contrast ($[\alpha]_D^{20}$ +24, *c* 0.43, ($CHCl_3$)) compared to natural rollicosin. Taking into account that the optical rotation of natural product was measured at low concentration, the difference may be due to experimental error. To clarify this, a direct comparison of our synthetic sample with the authentic natural product would be necessary. Therefore, we prepared the corresponding MTPA esters from synthetic **1** and **2** (Fig. 2).

The ^1H NMR chemical shifts of H-15 position of (*R*)-MTPA-**1** and (*R*)-MTPA-**2** showed clear difference (Table 1).

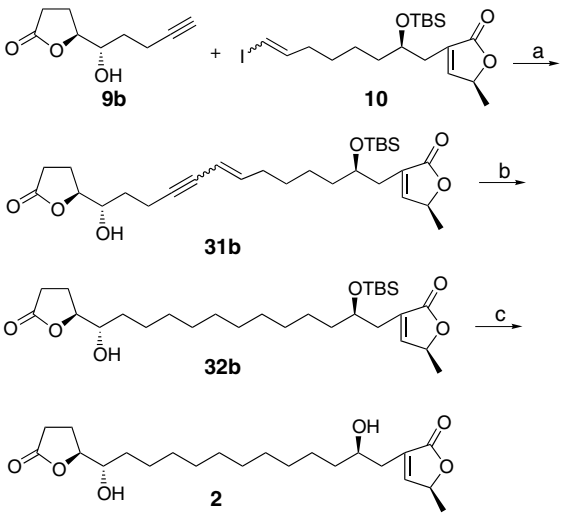
This indicates that if the bis-(*R*)-MTPA ester of natural **1** would be available, the absolute configuration of rollicosin (**1**) would be determined very clearly.



Scheme 3. Synthesis of the γ-lactone **10**. Reagents and conditions: (a) TBSCl, DMF, imidazole (89%); (b) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2AQN$, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH/H_2O, 0 °C (95%); (c) 2,2-dimethoxypropane, *p*-TsOH (93%); (d) TBAF, THF, 0 °C (94%); (e) i—MsCl, Et_3N, CH_2Cl_2; ii—NaI, $NaHCO_3$, acetone (85%); (f) lithium acetylide ethylenediamine complex, DMSO (73%); (g) i—*n*-Bu_3SnH, AIBN; ii—I_2, THF, 0 °C (92%); (h) concd HCl, MeOH (86%); (i) Tris–Cl, pyridine (98%); (j) NaH, THF (85%); (k) LiI, THF-H_2O-AcOH (93%); (l) TBSCl, imidazole, DMF (83%); (m) LDA, THF-HMPA (16%); (n) i—*m*CPBA, CH_2Cl_2; ii—toluene reflux (67%).



Scheme 4. Synthesis of **1**. Reagents and conditions: (a) 5 mol% $Cl_2Pd(PPh_3)_2$, 10 mol% CuI, Et_3N (86%); (b) *p*-$TsNHNH_2$, NaOAc, ethylene glycol diethyl ether (89%); (c) HF, CH_3CN (66%).



Scheme 5. Synthesis of **2**. Reagents and conditions: (a) 5 mol% $Cl_2Pd(PPh_3)_2$, 10 mol% CuI, Et_3N (67%); (b) *p*-$TsNHNH_2$, NaOAc, ethylene glycol diethyl ether (76%); (c) HF, CH_3CN (78%).

As to the synthesis of **3**, the hydroxyl lactone part **9a** was synthesized as described in Scheme 2. The α,β-unsaturated lactone **11** was prepared as shown in Scheme 6. 1,6-Hexanediol treated with 1.5 equiv of dihydropyrane in the presence of catalytic amount of *p*-TsOH afforded mono-THP alcohol **33**. Sulfonylation of the primary hydroxyl group in **33** with mesyl chloride afforded the sulfonate, which was then treated with NaI in the presence of sodium bicarbonate to give iodide **34**. Alkylation of **34** with lithium acetylide ethylenediamine complex gave terminal acetylene **35**. Compound **35** was treated with the Schwartz reagent[21] and subsequently iodine to afford an *E* vinyl iodide **36**. During the hydrozircona-

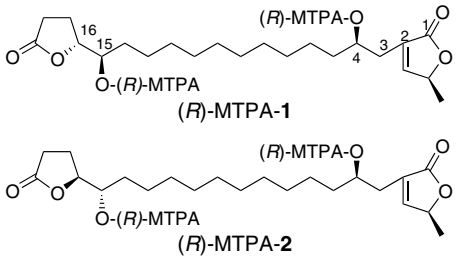


Figure 2. Bis-(*R*)-MTPA esters of **1** and **2**.

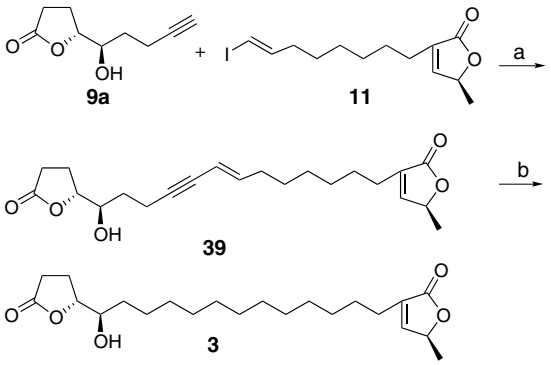
Table 1. ^{1}H NMR chemical shifts of the bis-(*R*)-MTPA esters of **1** and **2**

MTPA ester	15-H	16-H
(*R*)-MTPA-**1**	5.17	4.60
(*R*)-MTPA-**2**	5.08	4.60

tion, partial deprotection of the THP group occurred to afford **36**. Complete deprotection of the THP ether was performed using methanolic HCl to give **36**. Sulfonylation of the primary hydroxyl group of **36** with *p*-TsCl in pyridine afforded the sulfonate, which was then treated with NaI to give diiodide **37**. The lactone **38** was obtained in 50% yield by alkylation of the enolate prepared by mixing **12**[11] and NaHMDS with **37**. The α,β-unsaturated lactone **11** was obtained after oxidation of **38** with *m*CPBA followed by thermal elimination of sulfoxide under reflux in toluene (Scheme 6).

The segments **9a** and **11** were coupled by the Sonogashira cross-coupling reaction[16] to furnish cross-coupled product **39** in 58% yield. Diimide reduction with *p*-$TsNHNH_2$ and NaOAc in ethylene glycol diethyl ether under reflux afforded squamostolide **3** (Scheme 7).[17]

The optical rotation, melting point, ^{1}H NMR, and ^{13}C NMR spectra of the synthetic **3** were in good agreement with those of the reported values.



Scheme 7. Synthesis of **3**. Reagents and conditions: (a) 5 mol% $Cl_2Pd(PPh_3)_2$, 10 mol% CuI, Et_3N (58%); (b) *p*-$TsNHNH_2$, NaOAc, and ethylene glycol diethyl ether (62%).

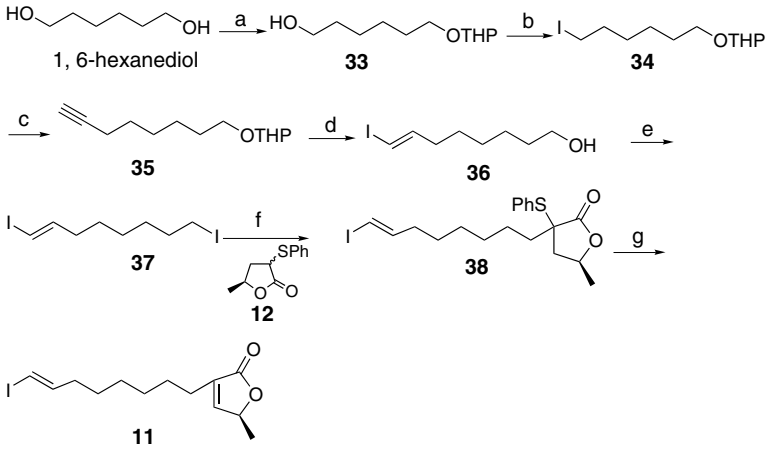
2.2. Inhibitory action with bovine heart mitochondrial complex I

Inhibitory effects of compounds **1**, **2**, and **3** on bovine heart mitochondrial complex I were examined according to the previous method (Table 2).[22] The IC_{50} values of **1**, **2**, and **3** were 660, 680, and 120 nM, respectively (Table 2).

Compounds **1** and **2** exhibited almost the same inhibitory potency, indicating that the stereochemistry around the hydroxylated lactone moiety does not affect the inhibitory action. It is noteworthy that compared to

Table 2. Inhibition activity of mitochondrial complex I

Sample	IC_{50} (nM)
1	660 ± 30
2	680 ± 30
3	120 ± 21
7	2.6 ± 0.2
Bullatacin	0.83 ± 0.06



Scheme 6. Synthesis of the γ-lactone part **11**. Reagents and conditions: (a) dihydropyrane, *p*-TsOH (67%); (b) i—*p*-TsCl, pyridine; ii—NaI, $NaHCO_3$, acetone (86%); (c) lithium acetylide ethylenediamine complex, DMSO (83%); (d) i—Cp_2ZrHCl, THF; ii—I_2, THF, 0 °C; iii—concd HCl, MeOH (81%); (e) i—*p*-TsCl, pyridine; ii—NaI, $NaHCO_3$, acetone (79%); (f) NaHMDS, THF-HMPA (45%); (g) i—*m*CPBA, CH_2Cl_2; ii—toluene reflux (67%).

potent natural acetogenins such as bullatacin (IC_{50} = 0.83 nM)[23] and *cis*-solamin (**7**) (IC_{50} = 2.6 nM),[24] **1** and **2** are much weaker inhibitors of the enzyme. Rollicosin and squamostolide do not have long hydrophobic alkyl tail which is one of the common structural features of a large number of natural acetogenins. However, this may not be a reason for the weak inhibitory activity since the long alkyl tail is not a crucial structural factor for the potent inhibition.[25] It is therefore clear that to maintain potent inhibitory effect, the hydroxylated lactone cannot substitute for the hydroxylated mono- or bis-THF with long alkyl tail that can be seen in ordinary acetogenins. From the comparison between rollicosin and squamostolide, it is indicated that the presence of a hydrophilic hydroxy group at the 4-position is unfavorable for the inhibitory action of this type of acetogenin, though it does not affect the activity in the case of ordinary acetogenins which inherently have a great hydrophobic nature.[22,23]

3. Conclusion

In conclusion, we have achieved total synthesis of (4*R*,15*R*,16*R*,21*S*)-rollicosin (**1**), (4*R*,15*S*, 16*S*,21*S*)-rollicosin (**2**), and squamostolide (**3**), and examined their inhibitory actions with bovine heart mitochondrial complex I. These compounds elicited much weaker activity compared to ordinary annonaceous acetogenins.

4. Experimental

4.1. General

All melting points are uncorrected. ^{1}H 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 constants were given in Hz. Mass spectra were obtained on JEOL JMS-HX211A and JMS-HX110A mass spectrometers. IR spectra were recorded with a JASCO FT-IR 480 Plus infrared spectrometer. Optical rotations were determined with a JASCO DIP-1000 polarimeter.

4.1.1. 7-Trimethylsilylhept-1-en-6-yn-3-ol (15). To a solution of vinylmagnesium chloride (1.6 M solution in THF, 50 ml, 80 mmol) was added aldehyde **14** (6.15 g, 40 mmol) at 0 °C. After stirring for 15 min, the reaction was quenched with saturated NH_4Cl (100 mL). The mixture was extracted with ether (4× 50 mL) and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (diethyl ether/pentane = 1:5) to give **15** (7.13 g, 98%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3357, 3082, 2958, 2175, 1644, 1427, 1250, 1054, 989, 843, 803. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.15 (9H, s), 1.79 (1H, d, J = 4.4 Hz, –OH), 2.35 (2H, m), 4.27 (1H, m), 5.14 (1H, d, J = 10.7 Hz), 5.27 (1H, d, J = 17.0 Hz), 5.87 (1H, ddd, J = 17.0, 10.7, 6.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.10, 16.18, 35.49, 72.15, 85.43, 106.72, 115.01, 140.39.

4.1.2. Ethyl (4*E*)-9-trimethylsilylnon-4-en-8-ynate (16). To a solution of 1, 1, 1-triethoxyethane (20 mL) were added alcohol **15** (2.99 g, 1.7 mmol) and two drops of propionic acid. After stirring for 9 h at 120 °C, the resulting mixture was cooled to room temperature and saturated $NaHCO_3$ (20 mL) was added to the mixture. The mixture was extracted with ether (4× 50 mL) and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 10:1) to give **16** (2.49 g, 64%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 2959, 2175, 1738, 1250, 1179, 1038, 970, 843, 760. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.14 (9H, s), 1.25 (3H, t, J = 7.1 Hz), 2.19–2.37 (4H, m), 4.13 (2H, q, J = 7.1 Hz), 5.49 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.08, 14.27, 20.23, 27.88, 31.73, 34.27, 60.27, 84.81, 106.86, 129.54, 129.60, 173.15.

4.1.3. (1′*R*,5*R*)-5-(5′-Trimethylsilyl-1′-hydroxypent-4′-ynyl)tetrahydrofuran-2-one (17a). To a suspension of AD mix β (2.74 g) in *t*-BuOH/H_2O (1:1, 20 mL) were added ester **16** (476 mg, 2.0 mmol) and methanesulfonamide (190 mg, 2.0 mmol). After stirring for 7 h at 0 °C, the reaction was quenched with half-saturated aqueous Na_2SO_3 solution (20 mL) and the mixture was extracted with EtOAc (2× 30 mL) and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 3:1) to give **17a** (453 mg, 94%) as a colorless oil. This compound showed a 98% ee by a ^{1}H NMR analysis of the corresponding Mosher ester derivative. $[\alpha]_D^{25}$ −1.87 (*c* 1.00, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3437, 2958, 2173, 1769, 1418, 1339, 1250, 1091, 1099, 1033, 984, 901, 843, 760. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.15 (9H, s), 1.75 (2H, m), 2.14–2.18 (3H, m), 2.28 (1H, m), 2.44 (2H, m), 2.52–2.63 (2H, m), 3.76 (1H, m), 4.45 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.07, 16.26, 24.05, 28.61, 31.64, 72.70, 72.36, 82.66, 85.95, 106.04, 176.93. FABHRMS calcd for $C_{12}H_{21}O_3Si$ [$(M+H)^+$], 241.1260, found, 241.1257.

4.1.4. (1′*S*,5*S*)-5-(5′-Trimethylsilyl-1′-hydroxypent-4′-ynyl)tetrahydrofuran-2-one (17b). This compound was prepared as just described above except for using AD mix α instead of AD mix β in 92% yield. This compound showed a 97% ee by a ^{1}H NMR analysis of the corresponding Mosher ester derivative. $[\alpha]_D^{25}$ +1.86 (*c* 1.43, $CHCl_3$). The IR, ^{1}H NMR, ^{13}C NMR, and MS spectra were identical with those of synthetic **17a**.

4.1.5. (1′*R*,5*R*)-5-(1′-Hydroxypent-4′-ynyl)tetrahydrofuran-2-one (9a). To a solution of lactone **17a** (453 mg, 1.89 mmol) in THF (10 mL) was added TBAF (1.0 M solution in THF, 3.8 ml, 3.8 mmol) at 0 °C. After stirring for 1 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with ether (2× 20 mL) and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (EtOAc) to give **9a** (301 mg, 95%) as a colorless oil. $[\alpha]_D^{20}$ −7.07 (*c* 1.23, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3421, 3286, 2934, 2173,

1760, 1418, 1347, 1187, 1099, 1086, 1055, 921, 645. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.75 (2H, m), 1.99 (1H, t, J = 2.6 Hz), 2.04 (1H, d, J = 11.4 Hz), 2.16 (1H, m), 2.29 (1H, m), 2.41 (2H, m), 2.55–2.65 (2H, m), 3.79 (1H, m), 4.45 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.78, 24.04, 28.61, 31.56, 69.34, 72.36, 82.71, 83.35, 176.86. CIHRMS calcd for $C_9H_{13}O_3$ [$(M+H)^+$], 169.0864, found, 169.0870.

4.1.6. (1′*S*,5*S*)-5-(1′-Hydroxypent-4′-ynyl)tetrahydrofuran-2-one (9b). This compound was prepared as just described above in 95% yield. $[\alpha]_D^{20}$ +7.27 (*c* 1.43, $CHCl_3$). The IR, ^{1}H NMR, ^{13}C NMR, and MS spectra were identical with those of synthetic **9a**.

4.1.7. (2*R*)-6-*tert*-Butyldimethylsilyloxyhexane-1,2-diol (19). To a suspension of $(DHQD)_2AQN$ (360 mg, 0.42 mmol), $K_2OsO_4{\cdot}2H_2O$ (51 mg, 0.17 mmol), $K_3Fe(CN)_6$ (42 g, 126 mmol), K_2CO_3 (17.4 g, 126 mmol), and methanesulfonamide (4.0 g, 42 mmol) in *t*-BuOH/H_2O (1:1, 120 mL) was added **18** (9.0 g, 42 mmol) in *t*-BuOH/H_2O (1:1, 50 mL) at 0 °C. After stirring for 26 h at 0 °C, the reaction was quenched with half-saturated aqueous Na_2SO_3 solution (20 mL) and the mixture was extracted with EtOAc (2× 30 mL) and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 3:1) to give **19** (9.86 g, 95%, 93% ee by a ^{1}H NMR analysis of the ester derived from (*S*)-(+)-MTPA chloride of **19**) as a colorless oil. $[\alpha]_D^{27}$ −0.02 (*c* 1.13, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3375, 2930, 2859, 1472, 1463, 1255, 1100, 837, 775. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.05 (6H, s), 0.89 (9H, s), 1.42 (2H, m), 1.49–1.57 (4H, m), 2.17 (1H, br, –OH), 2.37 (1H, br, –OH), 3.43 (1H, m), 3.61–3.72 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.27, 14.12, 21.89, 25.99, 32.61, 32.89, 63.06, 66.83, 72.24.

4.1.8. (2*R*)-1,2-(1′,2′-*O*-Isopropylidene)dioxy-6-*tert*-butyldimethylsilyloxyhexane (20). To a solution of diol **19** (9.86 g, 40 mmol) in dimethoxypropane (150 mL) was added *p*-TsOH (10 mg). After stirring for 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and the mixture was extracted with ether (2× 100 mL) and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 10:1) to give **20** (10.7 g, 93%) as a colorless oil. $[\alpha]_D^{27}$ −8.75 (*c* 1.06, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2985, 2934, 2859, 1472, 1461, 1378, 1369, 1254, 1100, 1063, 837, 775. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 1.35 (3H, s), 1.40 (3H, s), 1.45–1.65 (6H, m), 1.49–1.57 (4H, m), 3.50 (1H, m), 3.61 (2H, t, J = 6.5 Hz), 4.01–4.09 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.27, 18.36, 22.05, 25.78, 25.98, 26.70, 32.80, 33.36, 62.93, 69.50, 76.11 108.64.

4.1.9. (2*R*)-1,2-(1′,2′-*O*-Isopropylidene)dioxyhexan-6-ol (21). To a solution of **20** (10.7 g, 37.2 mmol) in THF (100 mL) was added TBAF (27.2 mL, 75 wt %, 74.4 mmol) at 0 °C. After stirring for 19 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (100 mL) and the mixture was extracted with ether (2× 100 mL) and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 3:1) to give **21** (6.1 g, 94%) as a colorless oil. $[\alpha]_D^{20}$ −13.1 (*c* 1.08, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3420, 3285, 2937, 2868, 1457, 1375, 1371, 1249, 1216, 1157, 1057, 855. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35 (3H, s), 1.41 (3H, s), 1.51–1.68 (6H, m), 3.51 (1H, m), 3.66 (2H, t, J = 6.5 Hz), 4.02–4.12 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.08, 25.75, 26.70, 32.65, 33.30, 62.74, 69.47, 76.04, 108.73.

4.1.10. (5*R*)-1-Iodo-5,6-(1′,2′-*O*-isopropylidene)dioxyhexane (22). To a solution of alcohol **21** (3.67 g, 21 mmol) and Et_3N (3.0 ml, 42 mmol) in CH_2Cl_2 (50 mL) was added MsCl (1.95 mL, 25 mmol) at −5 °C. After stirring for 10 min at this temperature, the reaction was quenched with saturated aqueous NH_4Cl (100 mL) and the mixture was extracted with ether (2× 50 mL) and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was dissolved in acetone (100 mL). To this solution, $NaHCO_3$(5.3 g, 63 mmol) and NaI (7.9 g, 53 mmol) were added at room temperature. After stirring for 18 h at room temperature, the reaction was quenched with H_2O (100 mL) and the mixture was extracted with ether (2× 100 mL) and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 10:1) to give **22** (5.07 g, 85%) as a colorless oil. This compound was used for the next step without further purification. $[\alpha]_D^{20}$ −5.49 (*c* 0.85, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2984, 2935, 2866, 1456, 1378, 1369, 1249, 1213, 1170, 1061, 856. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35 (3H, s), 1.41 (3H, s), 1.52–1.65 (4H, m), 1.85 (2H, m), 3.19 (2H, t, J = 7.0 Hz), 3.53 (1H, m), 4.03–4.11 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 6.44, 25.72, 26.78, 26.97, 32.53, 33.39, 69.41, 75.78, 108.82.

4.1.11. (2*R*)-1,2-(1′,2′-*O*-Isopropylidene)dioxyoct-7-yne (23). To a suspension of lithium acetylide, ethylenediamine complex (5.48 g, 54 mmol) in DMSO (150 mL) was added **22** (5.07 g, 17.9 mmol) in DMSO (20 mL) at 5 °C. After stirring for 18 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the mixture was extracted with ether (2× 100 mL) and the extract was washed with water and brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 10:1) to give **23** (2.38 g, 73%) as a colorless oil. $[\alpha]_D^{20}$ −10.1 (*c* 1.15, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3292, 2985, 2938, 2866, 1456, 1379, 1370, 1248 1216, 1156, 1059 858, 635. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35 (3H, s), 1.41 (3H, s), 1.51–1.62 (6H, m), 1.77 (1H, t, J = 2.4 Hz), 2.17–2.22 (2H, m), 3.52 (1H, m), 4.03–4.11 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.32, 24.92, 25.75, 26.97, 32.72, 33.10, 68.40, 69.45, 75.96, 84.28, 108.72. EIHRMS calcd for $C_{11}H_{18}O_2$ (M^+), 182.1307, found, 182.1311.

4.1.12. (7*EZ*,2*R*)-1,2-(1′,2′-*O*-Isopropylidene)dioxy-8-iodooct-7-ene (24). The acetylene **23** (2.38 g, 13 mmol) was treated with *n*-Bu_3SnH (4.12 mL, 15.7 mmol) and catalytic amount of AIBN (215 mg, 1.3 mmol) at 120 °C. After stirring for 3 h at this temperature, the mixture was diluted with THF (50 mL) and cooled to 0 °C. To this solution was added iodine (6.65 g, 26.2 mmol) in THF (50 mL). The reaction mixture was stirred for 1 h at 0 °C, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (50 mL) and the mixture was extracted with ether (2× 50 mL) and the extract was washed with water and brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 10:1) to give **24** (3.75 g, 92%, *E*/*Z* = 3 :1) as a colorless oil. IR (film) ν_{max} cm^{-1}: 2984, 2934, 2861, 1647, 1456, 1377, 1369, 1248 1215, 1156, 1059, 945, 857. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.35 (3H, s), 1.41 (3H, s), 1.59–1.64 (6H, m), 2.07–2.14 (2H, m), 2.17–2.22 (2H, m), 3.52 (1H, m), 4.01–4.09 (2H, m), 6.00 (0.75H, d, J = 14.3 Hz), 6.18 (0.5H, m), 6.50 (0.75H, dt, J = 14.3, 7.2 Hz). EIHRMS calcd for $C_{11}H_{19}IO_2$ (M^+), 310.0430, found, 310.0449.

4.1.13. (7*EZ*,2*R*)-8-Iodooct-7-ene-1,2-diol (25). To a solution of **24** (3.75 g, 12 mmol) was added three drops of concd HCl. After stirring for 2 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and the mixture was extracted with ether (2× 50 mL) and the extract was washed with water and brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 1:3) to give **25** (2.60 g, 86%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3368, 2933, 2857, 1647, 1456, 1103, 1053, 945, 869. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.40–1.97 (6H, m), 1.71 (1H, br, –OH), 1.77 (1H, br, –OH), 2.04–2.16 (2H, m), 3.48 (1H, m), 3.72 (2H, m), 4.03–4.11 (2H, m), 6.00 (0.75H, d, J = 14.5 Hz), 6.18 (0.5H, m), 6.50 (0.75H, dt, J = 14.5, 7.0 Hz). FABHRMS calcd for $C_{11}H_{19}IO_2$ [(M+H)$^+$], 271.1200, found, 271.1192.

4.1.14. (7*EZ*,2*R*)-1-(2′,4′,6′-Triisopropylbenzenesulfonyl)-8-iodooct-7-en-2-ol (26). To a solution of **25** (1.75 g, 6.5 mmol) in pyridine (40 mL) was added 2,4,6-triisopropylbenzenesulfonyl chloride (5.86 g, 19.4 mmol) at 0 °C. After stirring for 15 h at room temperature, the reaction was quenched with water (50 mL) and the mixture was extracted with ether (2× 50 mL) and the extract was washed with water and brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 3:1) to give **26** (3.38 g, 98%). IR (film) ν_{max} cm^{-1}: 3524, 2958, 2869, 1600, 1564, 1462, 1374, 1346, 1177, 1106, 968, 883, 810, 666. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.26 (6H, d, J = 6.5 Hz), 1.27 (6H, d, J = 6.5 Hz), 1.27 (6H, d, J = 6.5 Hz), 1.39–1.49 (4H, m), 1.71–1.75 (2H, m), 2.04–2.14 (2H, m), 2.92 (1H, m), 3.90–3.95 (2H, m), 4.05–4.15 (3H, m) 5.98 (0.75H, d, J = 14.5 Hz), 6.18 (0.5H, m), 6.48 (0.75H, dt, J = 14.5, 7.0 Hz), 7.20 (2H, s). FABHRMS calcd for $C_{23}H_{38}IO_4S$ [(M+H)$^+$], 537.5214, found, 537.5225.

4.1.15. (7*EZ*,2*R*)-1,2-Epoxy-8-iodooct-7-en (27). To a solution of NaH (606 mg, 25 mmol) in THF (50 mL) was added **26** (3.38 g, 6.3 mmol) in THF (20 mL) at 0 °C. After stirring for 19 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the mixture was extracted with ether (2× 50 mL) and the extract was washed with water and brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 5:1) to give **27** (1.36 g, 85%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3045, 2926, 2857, 1600, 1457, 1430, 1377, 1350, 1285, 1180, 1116, 943, 915, 834,807. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.47–1.52 (4H, m), 1.65–1.85 (2H, m), 2.08 (2H, m), 2.47 (1H, m), 2.74 (1H, m), 2.90 (1H, m), 6.00 (0.75H, d, J = 14.5 Hz), 6.17 (0.5H, m), 6.50 (0.75H, dt, J = 14.5, 7.0 Hz). EIHRMS calcd for $C_8H_{13}IO$ (M^+), 252.0011, found, 252.9996.

4.1.16. (7*EZ*,2*R*)-1,2-Diiodooct-7-en-2-ol (28). To a solution of **27** (1.36 g, 5.4 mmol) in THF (20 mL) were added LiI (613 mg, 22 mmol) and water (6 mL) at 0 °C. To this solution was added AcOH (30 mL). After stirring for 1 h at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (80 mL) and the mixture was extracted with ether (2× 50 mL) and the extract was washed with water and brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 5:1) to give **28** (1.91 g, 93%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3389, 2932, 2856, 1647, 1603, 1457, 1428, 1284, 1183, 1093, 1011, 945, 915, 807, 623. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.41–1.49 (4H, m), 1.73–1.84 (2H, m), 1.90 (1H, br, –OH), 2.08 (2H, m), 3.23 (1H, m), 3.38 (1H, m), 3.51 (1H, m), 6.01 (0.75H, d, J = 14.5 Hz), 6.18 (0.5H, m), 6.50 (0.75H, dt, J = 14.5, 7.0 Hz). FABHRMS calcd for $C_8H_{15}I_2O$ [(M+H)$^+$], 381.0172, found, 381.0164.

4.1.17. (7*EZ*,2*R*)-2-(*tert*-Butyldimethylsilyl)oxy-1,8-diiodooct-7-ene (29). To a solution of **28** (390 mg, 1.0 mmol) in DMF (20 mL) were added imidazole (279 mg, 4.1 mmol) and TBSCl (308 mg, 2.1 mmol). After stirring for 15 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with ether (2× 20 mL) and the extract was washed with water and brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 10:1) to give **29** (422 mg, 83%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3047, 2930, 2856, 1648, 1606, 1471, 1461, 1429, 1361, 1255, 1184, 1081, 1006, 940, 836, 805, 775. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.08 (3H, s), 0.09 (3H, s), 0.91 (9H, s), 1.39–1.63 (6H, m), 2.06 (2H, m), 3.18 (2H, m), 3.38 (1H, m), 3.55 (1H, m), 5.99 (0.75H, d, J = 14.4 Hz), 6.19 (0.5H, m), 6.50 (0.75H, dt, J = 14.4, 7.0 Hz). FABHRMS calcd for $C_{14}H_{29}I_2OSi$ [(M+H)$^+$], 495.2811, found, 495.2804.

4.1.18. (2′*R*,3*RS*,5*S*,7′*EZ*)-3-[2′-(*tert*-Butyldimethylsilyl)oxy-8′-iodo-7′-octenyl]-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (30). To a solution of *i*-Pr_2NH (0.14 mL, 0.94 mmol) in THF (2 mL) was added *n*-BuLi

(0.38 mL, 2.5 M solution in hexane, 0.94 mmol) at −10 °C. To this solution was added **29** (175 mg, 0.85 mmol) in THF (0.5 mL). After being stirred for 20 mim, **29** (422 mg, 0.85 mmol) in HMPA (0.45 mL) was added to the mixture at 0 °C. After stirring for 1 h at this temperature, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with ether (2× 20 mL) and the extract was washed with water and brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 5:1) to give **30** (80 mg, 16%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 2928, 2856, 1765, 1605, 1472, 1254, 1184, 1081, 1005, 835, 775. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.03 (0.75H, s), 0.04 (0.75H,s), 0.05 (2.25H, s), 0.12 (2.25H, s), 0.87 (2.25H, s), 0.90 (6.75H, s), 1.24 (2.25H, d, J = 6.2 Hz), 1.38 (0.75H, d, J = 6.2 Hz), 1.31–1.44 (4H, m), 1.73–1.76 (2H, m), 1.96–2.07 (4H, m), 3.00 (0.25H, m), 3.02 (0.75H, dd, J = 13.9, 7.6 Hz), 4.24 (2H, m), 4.51 (0.75H, m), 4.60 (0.25H, m), 5.98 (0.75H, d, J = 14.4 Hz), 6.18 (0.5H, m), 6.47 (0.75H, dt, J = 14.4, 7.0 Hz), 7.33–7.42 (3H, m), 7.54–7.57 (2H, m). FAB-HRMS calcd for $C_{25}H_{39}IO_3SSiI$ [$(M+H)^+$],575.1514, found, 575.1506.

4.1.19. (2*R*,5*S*,7′*EZ*)-3-[2′-(*tert*-Butyldimethylsilyl)oxy-8′-iodo-7′-octenyl]-5-methyl-2,3-dihydrofuran-2-one (10). To a solution of **30** (37 mg, 0.064 mmol) in CH_2Cl_2 (1 mL) was added *m*CPBA (80%, 21 mg, 0.064 mmol) at 0 °C. After the mixture had been stirred at this temperature for 10 min, $Na_2S_2O_3/NaHCO_3$ (1:1, 2 mL) was added. After stirring for 1 h, the mixture was extracted with ether (2× 10 mL) and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was dissolved in toluene (2 mL) and the solution was refluxed for 1 h. After completion of the reaction, concentration of the mixture afforded an oil, which was chromatographed over silica gel (hexane/EtOAc = 10:1) to give **10** (20 mg, 67 %) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3051, 2930, 2856, 2171, 1756, 1653, 1605, 1471, 1462, 1374, 1361, 1318, 1255, 1203, 1079, 1094, 1028, 949, 836, 775. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.03 (3H, s), 0.05 (3H, s), 0.87 (9H, s), 1.30–1.44 (6H, m), 1.44 (3H, d, J = 6.5 Hz), 2.04–2.05 (2H, m), 2.42 (2H, m), 3.96 (1H, m), 5.00 (1H, m), 5.98 (0.75H, d, J = 14.3 Hz), 6.15 (0.5H, m), 6.48 (0.75H, dt, J = 14.3, 6.5 Hz), 7.11 (1H, s). FABHRMS calcd for $C_{19}H_{34}O_3SiI$ [$(M+H)^+$], 465.1324, found, 465.1316.

4.1.20. (5″*R*,2′*R*,5*S*,7′*EZ*,13′*R*)-3-[2′-(*tert*-Butyldimethylsilyl)oxy-13′-hydroxy-13′-(tetrahydrofuran-2″-on-5″-yl)tridec-7′-ene-9′-ynyl]-5-methyl-2, 5-dihydrofuran-2-one (31a). To a solution of the vinyl iodide **10** (60 mg, 0.14 mmol) in Et_3N (0.5 mL) was added $Cl_2Pd(PPh_3)_2$ (2.8 mg, 0.007 mmol) and the resulting solution was stirred for 1 h. The acetylenic ether **9a** (60 mg, 0.14 mmol) along with CuI (1.4 mg, 0.014 mmol) was then added to the mixture. After being stirred for a further 8 h, the reaction was quenched with saturated aqueous NH_4Cl. The organic materials were extracted with ether and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/AcOEt = 4:1) to give **31** (87 mg, 86%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3460, 2930, 2856, 1755, 1462, 1360, 1319, 1254, 1189, 1081, 1028, 957, 836, 775. ^1H NMR (500 MHz, $CDCl_3$) δ: −0.01–0.07 (6H, m), 0.88 (9H, s), 1.36–1.38 (6H, m), 1.41 (3H, d, J = 6.8 Hz), 1.76 (2H, m), 2.07 (2H, m), 2.15 (2H, m), 2.29 (1H, m), 2.42 (2H, m), 2.50–2.67 (4H, m), 3.78 (1H, m), 3.95 (1H, m), 4.44 (1H, m), 5.01 (1H, m), 5.43 (0.89H, d, J = 15.7 Hz), 5.81 (0.22H, m), 6.03 (0.89H, dt, J = 15.7, 7.0 Hz), 7.12 (1H, s). FAB-HRMS calcd for $C_{28}H_{45}O_6Si$ [$(M+H)^+$], 505.2985, found, 505.2990.

4.1.21. (5″*S*,2′*R*,5*S*,7′*EZ*,13′*S*)-3-[2′-(*tert*-Butyldimethylsilyl)oxy-13′-hydroxy-13′-(tetrahydrofuran-2″-on-5″-yl)tridec-7′-ene-9′-ynyl]-5-methyl-2, 5-dihydrofuran-2-one (31b). This compound was prepared as just described above in 67% yield. $[\alpha]_D^{20}$ +7.27 (*c* 1.43, $CHCl_3$). The IR, ^1H NMR, ^{13}C NMR, and MS spectra were identical with those of synthetic **31a**.

4.1.22. (5″*R*,2′*R*,5*S*,13′*R*)-3-[2′-(*tert*-Butyldimethylsilyl)oxy-13′-hydroxy-13′-(tetrahydrofuran-2″-on-5″-yl)tridecanyl]-5-methyl-2, 5-dihydrofuran-2-one (32a). To a refluxing solution of **31** (15 mg, 0.20 mmol) and *p*-toluenesulfonylhydrazide (2.62 g, 13.4 mmol) in diethoxyethane (15 mL) was added sodium acetate (1.36 g, 16.6 mmol) in water (20 mL) over a 4 h period at 120 °C. After being cooled to room temperature, the reaction mixture was quenched with water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed over silica gel (hexane/AcOEt = 4:1) to give **32** (13 mg, 89%) as a colorless oil. $[\alpha]_D^{19}$ −3.6 (*c* 0.10, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3481, 2928, 2855, 1757, 1463, 1343, 1320, 1254, 1188, 1167, 1079, 1028, 837, 775. ^1H NMR (500 MHz, $CDCl_3$) δ: −0.01–0.07 (6H, m), 0.87 (9H, s), 1.24–1.54 (18H, m), 1.41 (3H, d, J = 6.8 Hz), 1.87 (1H, m), 2.10–2.17 (2H, m), 2.23–2.26 (2H, m), 2.42–2.45 (2H, m), 2.53–2.60 (2H, m), 3.57 (1H, m), 3.95 (1H, m), 4.42 (1H, m), 5.00 (1H, m), 7.12 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −4.42, 18.07, 18.99, 24.12, 25.08, 25.15, 25.45, 25.87, 25.91, 25.94, 25.98, 28.70, 29.48, 29.54, 29.68, 29.78, 32.76, 32.85, 33.01, 36.99, 70.27, 73.67, 77.47, 82.91, 125.92, 130.91, 151.48, 174.03, 177.07. FABHRMS calcd for $C_{28}H_{51}O_6Si$ [$(M+H)^+$], 511.3455, found. 511.3462.

4.1.23. (5″*S*,2′*R*,5*S*,13′*S*)-3-[2′-(*tert*-Butyldimethylsilyl)oxy-13′-hydroxy-13′-(tetrahydrofuran-2″-on-5″-yl)tridecanyl]-5-methyl-2, 5-dihydrofuran-2-one (32b). This compound was obtained as just described above in 76% yield. $[\alpha]_D^{22}$ +12.4 (*c* 0.15, $CHCl_3$). The IR, ^1H NMR, ^{13}C NMR, and MS spectra were identical with those of **31a**.

4.1.24. (15*R*,16*R*,4*R*,21*S*)-Rollicosin (1). To a solution of **32a** (13.7 mg, 0.027 mmol) in CH_3CN (1 mL) were added two drops of 46% HF at 0 °C. After being stirred for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted with ether and the extract was washed with brine. Drying

over $MgSO_4$ and the evaporation of the solvent gave a crude solid, which was purified with preparative TLC (AcOEt) to give a colorless solid. Recrystallization from hexane gave optically pure **1** (7.0 mg, 66%). Mp 104–106 °C, $[\alpha]_D^{24}$ +2.5 (*c* 0.29, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3420, 2923, 2851, 1748, 1458, 1321, 1192, 1084, 1026. ^1H NMR (500 MHz, $CDCl_3$,) δ: 1.20–1.60 (19H, m), 1.43 (3H, d, J = 6.8 Hz), 1.86 (1H, d, J = 5.8 Hz, –OH), 2.10–2.45 (4H, m), 2.23 (1H, br, –OH), 2.50–2.65 (3H, m), 3.57 (1H, m), 3.85 (1H, m), 4.41 (1H, td, J = 7.4, 4.5 Hz), 5.05 (1H, qd, J = 6.8, 1.4 Hz), 7.16 (1H, d, J = 1.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.13, 24.12, 25.41, 25.55, 28.70, 29.41, 29.47, 33.02, 33.40, 33.47, 37.44, 70.03, 73.69, 77.97, 82.90, 131.24, 151.79, 174.59, 177.05. FABHRMS calcd for $C_{22}H_{37}O_6$ [$(M+H)^+$],397.2590, found, 397.2601.

4.1.25. (15*S*,16*S*,4*R*,21*S*)-Rollicosin (2). Compound **2** was prepared as described above in 78% yield. Mp 91–92 °C. $[\alpha]_D^{20}$ +24 (*c* 0.43, $CHCl_3$). The IR, ^1H NMR, and ^{13}C NMR were identical with those of synthetic **1a**. FABHRMS calcd for $C_{22}H_{37}O_6$ [$(M+H)^+$], 397.2590, found, 397.2586.

4.1.26. (*E*)-8-Iodooct-6-en-1-ol (36). To a solution of **35** (1.05 g, 5 mmol) in THF was added Cp_2ZrHCl (1.55 g, 6 mmol) at 0 °C. After the mixture had been stirred for 2 h at room temperature, the solution of iodine (2.54 g, 10 mmol) in THF (10 mL) was added to the mixture at 0 °C and then stirred for further 1 h at room temperature. The reaction was quenched with saturated aqueous $Na_2S_2O_3$. The organic materials were extracted with ether and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was dissolved in MeOH (5 mL) and treated with a trace of concd HCl. After the mixture had been stirred for 5 h, the solvent was evaporated and the crude product was purified with silica gel column chromatography with hexane/AcOEt = 4:1 as an eluent to afford **36** (1.03 g, 81%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3371, 2940, 2855, 1600, 1463, 1060, 945. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.25–1.60 (8H, m), 2.02–2.06 (2H, m), 3.64 (2H, m), 3.95 (1H, m), 5.96 (1H, dt, J = 14.4, 1.2 Hz), 6.51 (1H, dt, J = 14.1, 7.2 Hz). EIHRMS calcd for $C_8H_{15}OI$ (M^+), 254.0169, found. 254.0140.

4.1.27. (*E*)-1,8-Diodooct-1-ene (37). To an ice-cooled solution of **36** (1.02 g, 4 mmol) in pyridine (5 mL) was added *p*-TsCl (953 mg, 5 mmol). After being stirred for 1 h at 0 °C and then at room temperature for 5 h, the mixture was diluted with ether and washed with 1 N HCl and water. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was dissolved in acetone (10 mL) and treated with NaI (1.50 g, 10 mmol). After the mixture had been stirred for 6 h, the solvent was evaporated and the crude product was purified with silica gel column chromatography with hexane/AcOEt = 20:1 as an eluent to afford **37** (1.15 g, 79%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3050, 2940, 2855, 1600, 1463, 1430, 1280, 1200, 1060, 945. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.25–1.55 (4 H, m), 1.78–1.85 (4H, m), 2.02–2.07 (2H, m), 3.19 (2H, t, J = 7.0 Hz), 5.97 (1H, dt, J = 14.4, 1.2 Hz), 6.50 (1H, dt, J = 14.1, 7.2 Hz). EIHRMS calcd for $C_8H_{14}I_2$ (M^+), 363.9185, found, 363.9204.

4.1.28. (3*RS*,5*S*,7*E*)-3-[8′-Iodooct-7′-enyl]-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (38). To an ice-cooled solution of **12** (200 mg, 1 mmol) in THF (5 mL) was added NaHMDS (0.6 M solution in toluene, 2.0 mL). After the mixture had been stirred for 20 min at 0 °C, the diiodide **37** (382 mg, 1 mmol) in HMPA (2 mL) was added to it at 0 °C and the whole was allowed to warm to 23 °C. After stirring for 1 h at this temperature, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with ether (2× 20 mL) and the extract was washed with water and brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/EtOAc = 5:1) to give **38** (225 mg, 45%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3020, 2928, 2856, 1765, 1605, 1472, 1254, 1184, 1081, 1005, 835, 775; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.19 (2.25H, d, J = 6.2 Hz), 1.38 (0.75 H, d, J = 6.2 Hz), 1.20–1.80 (10H, m), 1.96 (1H, m), 2.02–2.20 (2H, m), 2.31–2.35 (0.25H, dd, J = 13.7, 5.4 Hz), 2.48–2.53 (0.75H, dd, J = 14.9, 7.6 Hz), 4.51 (0.75H, m), 4.60 (0.25H, m), 5.98 (1H, d, J = 14.4 Hz), 6.47 (1H, dt, J = 14.4, 7.0 Hz), 7.33–7.42 (3H, m), 7.54–7.57 (2H, m). EIHRMS calcd for $C_{19}H_{25}IO_2S$ (M^+) 444.0620, found, 444.0605.

4.1.29. (5*S*,7*E*)-3-[8′-Iodooct-7′-enyl]5-methyl-2,3-dihydrofuran-2-one (11). To a solution of **38** (28 mg, 0.064 mmol) in CH_2Cl_2 (1 ml) was added *m*CPBA (80%, 21 mg, 0.064 mmol) at 0 °C. After the mixture had been stirred at this temperature for 10 min, $Na_2S_2O_3/NaHCO_3$ (1:1, 2 mL) was added. After stirring for 1 h, the mixture was extracted with ether (2× 10 mL) and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was dissolved in toluene (2 mL) and the solution was refluxed for 1 h. After completion of the reaction, concentration of the mixture afforded an oil, which was chromatographed over silica gel (hexane/EtOAc = 10:1) to give **11** (20 mg, 67%) as a colorless oil, $[\alpha]_D^{24}$ +34 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3058, 2976, 2930, 2855, 1764, 1604, 1439, 1342, 1186, 1094, 946, 751, 693; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.41 (3H, d, J = 6.9 Hz), 1.47–1.60 (8H, m), 2.04–2.05 (2H, m), 2.26 (2H, m), 4.99 (1H, qd, J = 6.9, 1.5 Hz), 5.99 (1H, d, J = 14.3 Hz), 6.50 (1H, dt, J = 14.3, 6.5 Hz), 6.98 (1H, d, J = 1.5 Hz). EIHRMS calcd for $C_{13}H_{19}O_2I$ (M^+), 334.0432, found, 334.0415.

4.1.30. (2″*R*,2″*S*,5*S*,7′*E*,13′*R*)-3-[13′-Hydroxy-13′-(tetrahydrofuran-2″-on-5″-yl)tridec-7′-ene-9′-ynyl]-5-methyl-2,5-dihydrofuran-2-one (39). To a solution of the vinyl iodide **11** (90 mg, 0.27 mmol) in benzene (1 mL) and Et_3N (0.08 mL, 0.54 mmol) was added $Cl_2Pd(PPh_3)_2$ (10 mg, 0.0135 mmol) and the resulting solution was stirred for 1 h. The acetylenic ether **7** (60 mg, 0.14 mmol) along with CuI (5 mg, 0.027 mmol) was then added to the mixture, which after being stirred for a further 8 h, the reaction was quenched with saturated aqueous NH_4Cl. The

organic materials were extracted with ether and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane/AcOEt = 4:1) to give **39** (58 mg, 58%) as a colorless oil. $[\alpha]_D^{23}$ +2.27 (*c* 0.50, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3460, 2929, 2856, 2215, 1752, 1456, 1320, 1192, 1084, 1025, 957. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.39 (3H, d, J = 6.8 Hz), 1.45–1.60 (10H, m), 1.76 (2H, m), 2.00–2.17 (2H, m), 2.27 (4H, m), 2.48–2.67 (3H, m), 3.78 (1H, m), 4.45 (1H, m), 4.99 (1H, m), 5.42 (1H, d, J = 15.9 Hz), 6.03 (1H, dt, J = 15.9, 7.0 Hz), 6.97 (1H, s).^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.68, 19.20, 24.04, 25.13, 27.33, 28.58, 28.62, 28.68, 28.93, 31.78, 32.84, 72.56, 77.39, 80.31, 82.72, 87.02, 109.57, 134.25, 143.89, 148.89, 173.82, 176.90. FABHRMS calcd for $C_{22}H_{31}O_5$ [$(M+H)^+$], 375.2171, found, 375.2167.

4.1.31. Squamostolide (3). To a refluxing solution of **39** (18 mg, 0.045 mmol) and *p*-toluenesulfonylhydrazide (0.6 g, 4.6 mmol) in diethoxyethane (15 mL) was added sodium acetate (315 mg, 3.8 mmol) in water (5 mL) over a 4 h period at 120 °C. After being cooled to room temperature, the reaction mixture was quenched with water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with preparative TLC (toluene/AcOEt = 4:1) to give **3** (10 mg, 62%) as a colorless solid. Mp 92–93 °C, (lit., 94–96 °C).[3] $[\alpha]_D^{22}$ −3.27 (*c* 0.10, acetone), {lit., $[\alpha]_D^{24}$ −3.3 (*c* 0.122, acetone)}.[3] IR (film) ν_{max} cm^{-1}: 3400, 3071, 2917, 2849, 1740, 1471, 1323, 1254, 1190, 1083, 1030; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.25–1.55 (22H, m), 1.39 (3H, d, J = 6.8 Hz), 1.85 (1H, br, –OH), 2.09–2.30 (3H, m), 2.51–2.62 (2H, m), 3.57 (1H, m), 4.41 (1H, m), 4.98 (1H, dq, J = 6.8, 1.2 Hz), 6.98 (1H, d, J = 1.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.21, 24.09, 25.17, 25.43, 27.41, 28.68, 29.16, 29.26, 29.46, 29.50, 29.53, 32.99, 73.67, 77.38, 82.87, 134.36, 148.84, 173.88, 177.03. FABHRMS calcd for $C_{22}H_{37}O_5$ [$(M+H)^+$], 381.2641, found, 381.2631.

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

Acknowledgments

We thank Professor Yang-Chang Wu (Kaohsiung Medical University, Taiwan) for providing ^1H and ^{13}C NMR spectra of natural rollicosin. This work was supported in part by a Grant-in-aid from the Japan Society for the Promotion of Science (15780084). We thank Ms. Keiko Hashimoto and Ms. Megumi Miyazawa of the Faculty of Agriculture, Shinshu University, for the 500 MHz NMR measurements.

References and notes

1. For recent reviews for Annonaceous acetogenins, see: Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303.
2. Liaw, C.-C.; Chang, F.-R.; Wu, M.-J.; Wu, Y.-C. *J. Nat. Prod.* **2003**, *66*, 279–281.
3. Xie, H. H.; Wei, X. Y.; Wang, J. D.; Liu, M. F.; Yang, R. Z. *Chin. Chem. Lett.* **2003**, *14*, 588–590.
4. Myint, S. H.; Laurens, A.; Hocquemiller, R.; Cavé, A.; Davoust, D.; Cortes, D. *Heterocycles* **1990**, *31*, 861–867.
5. Woo, M. H.; Ye, Q.; Gu, Z.-M.; Zhao, G.-X.; McLaughlin, J. L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1135–1140.
6. Myint, S. H.; Cortes, D.; Laurens, A.; Hocquemiller, R.; Leboeuf, M.; Cavé, A.; Cotte, J.; Quero, A.-M. *Phytochemistry* **1991**, *30*, 3335–3338.
7. Gleye, C.; Duret, P.; Laurens, A.; Hocquemiller, R.; Cavé, A. *J. Nat. Prod.* **1998**, *61*, 576–579.
8. For isolation: (a) Rieser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett.* **1991**, *32*, 1137–1140, For synthesis: (b) Keinan, E.; Sinha, S.; Anjana, S. B.; Wang, Z. M.; Zhang, X. L.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 6307–6410; (c) Makabe, H.; Tanaka, A.; Oritani, T. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 1028–1029.
9. For preliminary communication of the synthesis of (4*R*,15*R*,16*R*,21*S*)-rollicosin (**1**), (4*R*,15*S*,16*S*,21*S*)-rollicosin (**2**) and their inhibitory action of mitochondrial complex I: (a) Makabe, H.; Higuchi, M.; Konno, H.; Murai, M.; Miyoshi, H. *Tetrahedron Lett.* **2005**, *46*, 4671–4675; (b) Quinn, K. J.; Isaacs, A. K.; DeChristopher, B. A.; Szklarz, S. C.; Arvary, R. A. *Org. Lett.* **2005**, *7*, 1243–1245.
10. (a) Lee, J.-L.; Lin, C.-F.; Hsieh, L.-Y.; Chiu, H.-F.; Wu, Y.-C.; Wang, K.-S.; Wu, M.-J. *Tetrahedron Lett.* **2003**, *44*, 7833–7835; (b) Lee, C.-L.; Lin, C.-F.; Lin, W.-R.; Wang, K.-S.; Chang, Y.; Lin, S.-R.; Wu, Y.-C.; Wu, M.-J. *Bioorg. Med. Chem.* **2005**, *13*, 5864–5872.
11. White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991–4998.
12. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.
13. Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 448–451.
14. Hu, T.-S.; Yu, Q.; Wu, Y.-L.; Wu, Y. *J. Org. Chem.* **2001**, *66*, 853–861.
15. Yang, W.-Q.; Kitahara, T. *Tetrahedron Lett.* **1999**, *40*, 7827–7830.
16. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.
17. Makabe, H.; Miyawaki, A.; Takahashi, R.; Hattori, Y.; Konno, H.; Abe, M.; Miyoshi, H. *Tetrahedron Lett.* **2004**, *45*, 973–977.
18. The proton chemical shifts of C-4 and C-15 showed 3.85 and 3.57 ppm in the ^1H NMR spectrum kindly provided by Prof. Y.-C. Wu. Those of reported values were 3.75 and 3.48 ppm, respectively. There might be some miswriting in

the ^{1}H NMR of **1** in Ref. 2. After submission of previous communication (Ref. 9a), the paper of K.J. Quinn and coworkers appeared in Ref. 9b, in which they reported the synthesis of **1** through a procedure different from ours. The ^{1}H and ^{13}C NMR of **1** synthesized by us matched very well with those by K. J. Quinn and coworkers.

19. The discrepancy in the optical rotation value of the synthetic product with that reported for the natural product has been reported (a) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067–7073; (b) Takahashi, S.; Kubota, A.; Nakata, T. *Org. Lett.* **2003**, *5*, 1353–1356; (c) Ref. 17.
20. The relative stereochemistry of the hydroxy lactone moiety (15,16 position of 1) can be determined by ^{1}H and ^{13}C NMR. We also prepared 15-*epi*-1 (15,16-*erythro*) from **9a**. The ^{1}H and ^{13}C NMR data for 15-*epi*-**1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.20–1.65 (19H, m), 1.43 (3H, d, J = 6.8 Hz), 1.96 (1H, br, –OH), 2.10–2.45 (4H, m), 2.24 (1H, br, –OH), 2.45–2.65 (3H, m), 3.85 (1H, m), 3.92 (1H, m), 4.42 (1H, td, J = 7.4, 4.5 Hz), 5.05 (1H, qd, J = 6.8, 1.4 Hz), 7.16 (1H, d, J = 1.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.12, 21.17, 25.41, 25.55, 28.70, 29.41, 29.47, 31.98, 33.41, 33.46, 37.43, 69.99, 71.49, 77.98, 82.82, 131.23, 151.81, 174.59, 177.38.
21. Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115–8116.
22. Miyoshi, H.; Ohshima, M.; Shimada, H.; Akagi, T.; Iwamura, H.; McLaughlin, J. L. *Biochim. Biophys. Acta* **1998**, *1365*, 443–452.
23. Abe, M.; Murai, M.; Ichimaru, N.; Kenmochi, A.; Yoshida, T.; Kubo, A.; Kimura, Y.; Moroda, A.; Makabe, H.; Nishioka, T.; Miyoshi, H. *Biochemistry* **2005**, *44*, 14898–14906.
24. Makabe, H.; Hattori, Y.; Kimura, Y.; Konno, H.; Abe, M.; Miyoshi, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **2004**, *60*, 10651–10657.
25. Motoyama, T.; Yabunaka, H.; Miyoshi, H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2089–2092.
26. Matsuno-Yagi, A.; Hatefi, Y. *J. Biol. Chem.* **1985**, *260*, 14424–14427.