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Synthesis of (4*R*,15*R*,16*R*,21*S*)- and (4*R*,15*S*,16*S*,21*S*)-rollicosin

Hidefumi Makabe,[a,*] Masaharu Higuchi,[a] Hiroyuki Konno,[b] Masatoshi Murai[c] and Hideto Miyoshi[c]

[a]*Sciences of Functional Foods, Graduate School of Agriculture, Shinshu University, 8304 Minami-minowa, Kamiina, Nagano 399-4598, Japan*
[b]*Department of Chemistry, Graduate School of Medical Sciences, Kyoto Prefectural University of Medicine, Kita-ku, Kyoto 603-8334 Japan*
[c]*Division of Applied Life Sciences, Graduate School of Agriculture, Kyoto University, Kita-shirakawa, Sakyo-ku, Kyoto 606-8502, Japan*

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Abstract—A convergent synthesis of (4*R*,15*R*,16*R*,21*S*)-rollicosin (**1**) and (4*R*,15*S*,16*S*,21*S*)-rollicosin (**2**) was accomplished. Hydroxy lactone **6a** and/or **6b** were synthesized from 4-pentyn-1-ol, and α,β-unsaturated lactone **7** was synthesized from γ-lactone **8** and 5-hexen-1-ol. Inhibitory activity of these compounds was examined with bovine heart mitochondrial complex I.

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, antiparasitic, and antifeedant. So far, more than 400 compounds have been isolated.[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] This compound possesses a partial skeleton of *A. acetogenins* containing two γ-lactone moieties on both sides of an aliphatic chain. Rollicosin may be generated from oxidative degradation of classical acetogenins such as murisolin (**3**)[3] and *cis*-murisolin (**4**).[4] Moreover, this compound may help investigate the role of the terminal hydroxylated lactone moiety for its bioactivity in stead of the hydroxylated THF moiety with long aliphatic chain that can be seen in the classical acetogenins. The absolute stereochemistry of **1** 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 **1** were determined by comparison of optical rotation between **1** and (−)-muricatacin (**5**).[5] Recently, rollicosin analogue, (15*S*,16*S*,21*R*)-4-deoxyrollicosin was synthesized by Wu and co-workers[6] (Fig. 1).

In this letter, we wish to report the synthesis of (4*R*,15*R*,16*R*,21*S*)-rollicosin (**1**) and (4*R*, 15*S*,16*S*,21*S*)-rollicosin (**2**) and their inhibitory activity against bovine mitochondrial complex I.

Scheme 1 outlines our synthetic strategy. The target compound **1** would be derived from hydroxy lactone **6a** and the α,β-unsaturated lactone **7**. Hydroxy lactone **6a** could be synthesized from 4-pentyn-1-ol by application of Wu and co-workers.[6] Synthesis of **7** could be accomplished by 5-hexen-1-ol and γ-lactone **8** which could be prepared by White et al.'s method.[7]

As shown in Scheme 2, the hydroxy lactone **6a** was constructed via a six-step process using Wu and co-workers method[6] with slight modification. The synthesis was started from 4-pentyn-1-ol, which was treated with trimethylsilyl chloride to afford alcohol **9**. Compound **9** was oxidized with SO_3 pyridine to give aldehyde **10**, which was reacted with vinylmagnesium chloride to afford allylic alcohol **11**. Johnson–Claisen rearrangement of **11** with triethyl orthoacetate and a catalytic amount of propionic acid gave **12**, followed

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* Corresponding author. Tel.: +81 265 77 1630; fax: +81 265 77 1700; e-mail: makabeh@gipmc.shinshu-u.ac.jp

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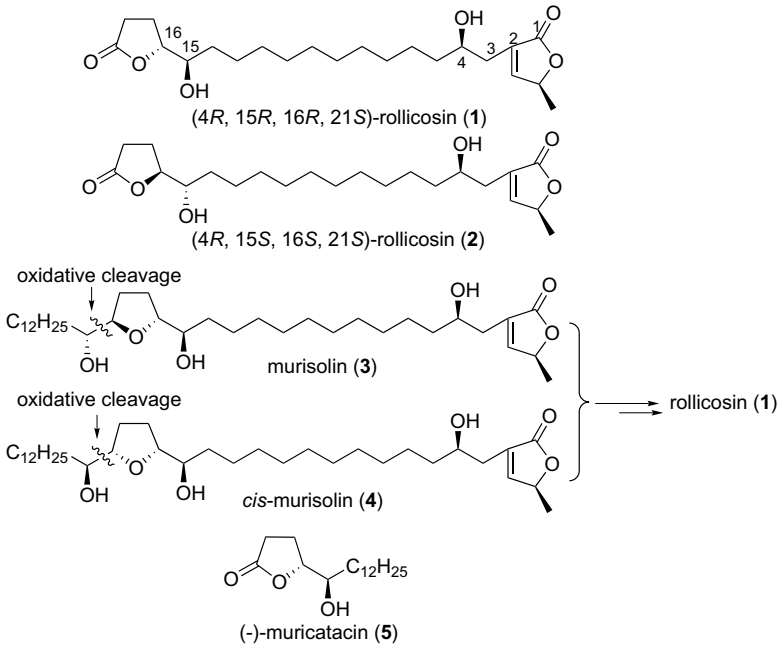
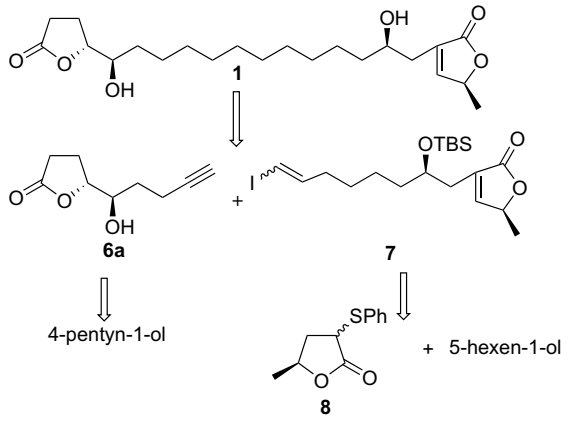


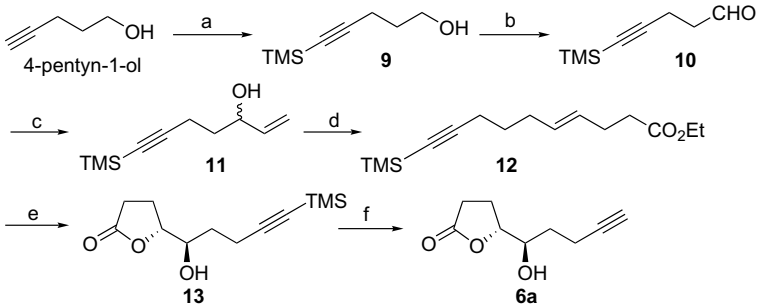
Figure 1. The structure of rollicosin.



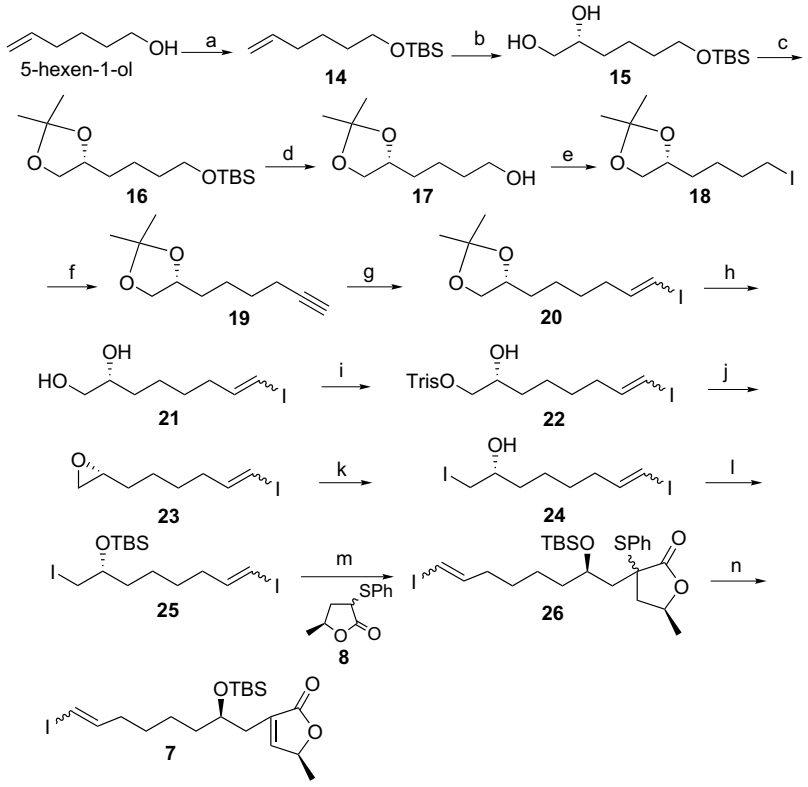
Scheme 1. Synthetic strategy of rollicosin.

by Sharpless asymmetric dihydroxylation using AD mix β[8] to furnish lactone **13**. Removal of TMS group of **13** with TBAF gave hydroxy lactone **6a**.

The α,β-unsaturated lactone **7** was prepared as shown in Scheme 3. 5-Hexen-1-ol was treated with TBSCl and imidazole in DMF afforded the silyl ether **14**. Sharpless asymmetric dihydroxylation of **14** using $(DHQD)_2AQN$ as a ligand[9] gave diol **15**, which showed 93% ee based on a ^1H NMR analysis of the corresponding Mosher ester derivative. The 1,2-diol of **15** was protected as an acetonide with dimethoxypropane in the presence of *p*-TsOH to furnish **16**. Deprotection of the TBS group with TBAF gave **17**. Compound **17** was transformed into iodide **18** via mesylation followed by iodination. Alkylation of **18** with lithium acetylide, ethylenediamine complex gave terminal acetylene **19**. Compound **19** was treated with *n*-Bu_3SnH and subsequently iodine to afford an *EZ* mixture (*E*/*Z* = 8/1) of vinyl iodide **20**. Deprotection of the acetonide group of **20** with methanolic HCl gave diol **21**. Selective sulfonylation of the primary hydroxyl group in **21** with triisopropylbenzenesulfonyl chloride in pyridine afforded the sulfonate **22**, which was then treated with NaH in THF to give epoxide **23**. Iodination of **23** with LiI gave hydroxyl



Scheme 2. Synthesis of hydroxy lactone **6a** of **1**. 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 (99%); (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%).

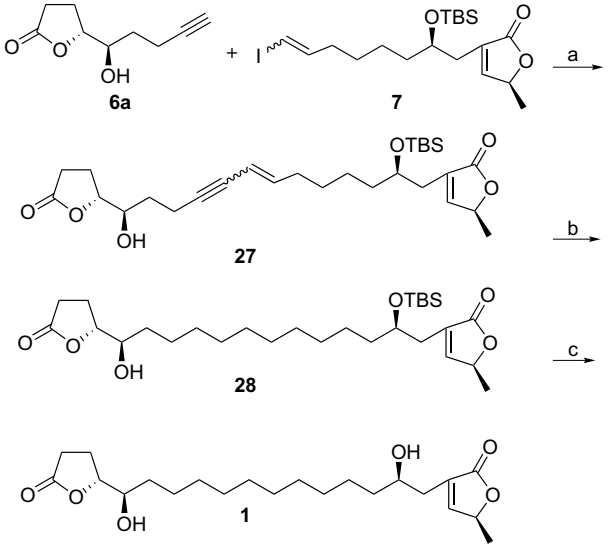


Scheme 3. Synthesis of the γ-lactone part **7** of **1**. Reagents and conditions: (a) TBSCl, DMF, imidazole (89%); (b) $(DHQD)_2AQN$, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH/H_2O, 0 °C (95%); (c) dimethoxypropane, *p*-TsOH (93%); (d) TBAF, THF, 0 °C (94%); (e) (i) MsCl, Et_3N, CH_2Cl_2; (ii) NaI, $NaHCO_3$, 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) TrisCl, pyridine (98%); (j) NaH, THF (85%); (k) LiI, THF–water–AcOH (93%); (l) TBSCl, imidazole, DMF (83%); (m) LDA, THF–HMPA (16%); (n) (i) *m*-CPBA; (ii) toluene, reflux (67%).

iodide **24**, protection of the alcohol with TBSCl gave **25**.[10] The lactone **26** was obtained in 16% yield by alkylation of the enolate prepared by mixing **8**[4] and LDA with **25**. Unreacted **8** and **25** were recovered in 70% and 71% yield, respectively. These compounds could be used for the same reaction again. The α,β-unsaturated lactone **7** was obtained after oxidation of **26** with *m*-CPBA followed by thermal elimination of sulfoxide under reflux in toluene.

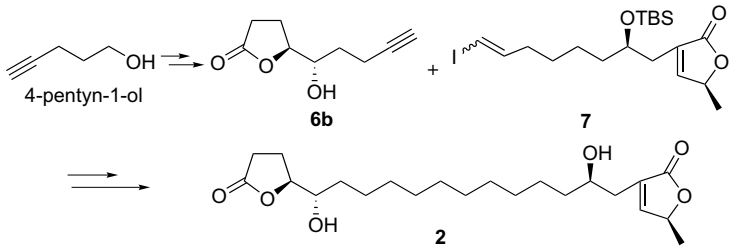
Both segments were coupled by the Sonogashira cross-coupling reaction[11] to furnish cross-coupled product **27** in 64% yield. Diimide reduction with *p*-$TsNHNH_2$ and NaOAc in ethylene glycol diethyl ether under reflux afforded saturated product **28**.[12] Finally, deprotection of TBS ethers with HF afforded **1** (Scheme 4).[13]

The ^1H NMR and ^{13}C NMR spectra of the synthetic **1** were in good agreement with those of natural **1** kindly provided by Professor Wu.[14] 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 **1** was reported to be −26.0 (*c* 0.05, $CHCl_3$).[15] Therefore we also prepared (4*R*,15*S*,16*S*,21*S*)-rollicosin (**2**), which has same relative stereochemistry (15,16-*threo*) of **1**,[16] starting from **6b** using the same procedure as that employed for **1** (Scheme 5).[17]



Scheme 4. Synthesis of **1**. Reagents and conditions: (a) 5 mol% $Cl_2Pd(PPh_3)_2$, 10 mol% CuI, Et_3N (64%); (b) *p*-$TsNHNH_2$, NaOAc, ethylene glycol diethyl ether (96%); (c) HF, CH_3CN (85%).

The specific rotation of **2** showed sharp contrast ($[\alpha]_D^{20}$ +24 (*c* 0.43, $CHCl_3$)) compared to natural **1**. Taking into account that the optical rotation of natural product was measured at low concentration, the



Scheme 5. Synthesis of **2**.

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 ^{1}H 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.

Inhibitory effect of **1** and **2** on bovine heart mitochondrial complex I (NADH-ubiquinone oxidoreductase) was examined according to the previous method.[18] Both compounds exhibited almost the same inhibitory potency (**1**: IC_{50} = 0.66±0.03 μM, **2**: IC_{50} = 0.68±0.03 μM), indicating that the stereochemistry around the hydroxylated lactone moiety does not affect the inhibitory action. It is noteworthy that compared to potent natural acetogenins like bullatacin (IC_{50} = 0.8 nM), both compounds are much weaker inhibitors of the enzyme. Rollicosin does not have a 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.[19] We therefore conclude that the hydroxylated lactone cannot be substituted for the hydroxylated mono- or bis-THF ring moiety of ordinary acetogenins for the activity.

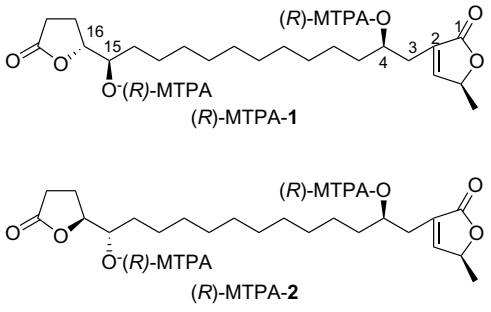


Figure 2. Bis-(*R*)-MTPA esters of **1** and **2**.

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

In summary, we have achieved total synthesis of (4*R*,15*R*,16*R*,21*S*)-rollicosin (**1**) and (4*R*,15*S*,16*S*,21*S*)-rollicosin (**2**). Inhibitory action of these compounds was examined with bovine heart mitochondrial complex I. Both compounds showed almost the same activity.

Acknowledgements

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13. The data for compound **1a**: 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 ($CDCl_3$, Me_4Si) 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 ($CDCl_3$, Me_4Si) 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. HRFABMS (M+H): calcd for $C_{22}H_{36}O_6$: 397.2592. Found 397.2601.
14. 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 Professor Y.-C. Wu. Those of reported values were 3.75 and 3.48 ppm, respectively. There might be some miswriting in the ^1H NMR of **1** in Ref. 2. After submission of this manuscript, the paper by K. J. Quinn and co-workers appeared in *Org. Lett.* **2005**, *7*, 1243–1245, in which they reported the synthesis of **1** through a procedure different from ours. The ^1H and ^{13}C NMR of **1** synthesized by us matched very well with those by K. J. Quinn and co-workers.
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16. The relative stereochemistry of hydroxy lactone moiety (15,16 position of **1**) can be determined by ^1H and ^{13}C NMR. We also prepared 15-*epi*-**1** (15,16-*erythro*) from **6a**. The ^1H and ^{13}C NMR data for 15-*epi*-**1**: ^1H NMR ($CDCl_3$, Me_4Si) 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 ($CDCl_3$, Me_4Si) 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.
17. The data for compound **2**: mp 91–92 °C, $[\alpha]_D^{20}$ +24 (*c* 0.43, $CHCl_3$). The IR, ^1H NMR, ^{13}C NMR were identical with those of synthetic **1**. HR-FABMS (M+H): calcd for $C_{22}H_{36}O_6$: 397.2592. Found 397.2586.
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