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

Shin-ichi Furuhata [a], Yasunao Hattori [b,c], Motonori Okajima [a], Hiroyuki Konno [d], Masato Abe [e], Hideto Miyoshi [e], Tetsuhisa Goto [b,f], Hidefumi Makabe [a,*]

[a] Sciences of Functional Foods, Graduate School of Agriculture, Shinshu University, 8304 Minami-minowa, Kami-ina, Nagano 399-4598, Japan
[b] Interdisciplinary Graduate School of Science and Technology, Shinshu University, 8304 Minami-minowa, Kami-ina, Nagano 399-4598, Japan
[c] Satellite Venture Business Laboratory, Shinshu University, 3-15-1 Tokida, Ueda, Nagano 386-8567, Japan
[d] Department of Chemistry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kita-ku, Kyoto 603-8334, Japan
[e] Division of Applied Life Sciences, Graduate School of Agriculture, Kyoto University, Kita-shirakawa, Sakyo-ku, Kyoto 606-8502, Japan
[f] Department of Bioscience and Biotechnology, Faculty of Agriculture, Shinshu University, 8304 Minami-minowa, Kami-ina, Nagano 399-4598, Japan

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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**)

* Corresponding author. Tel.: +81 265 77 1630; fax: +81 265 77 1700.
E-mail address: makabeh@shinshu-u.ac.jp (H. Makabe).

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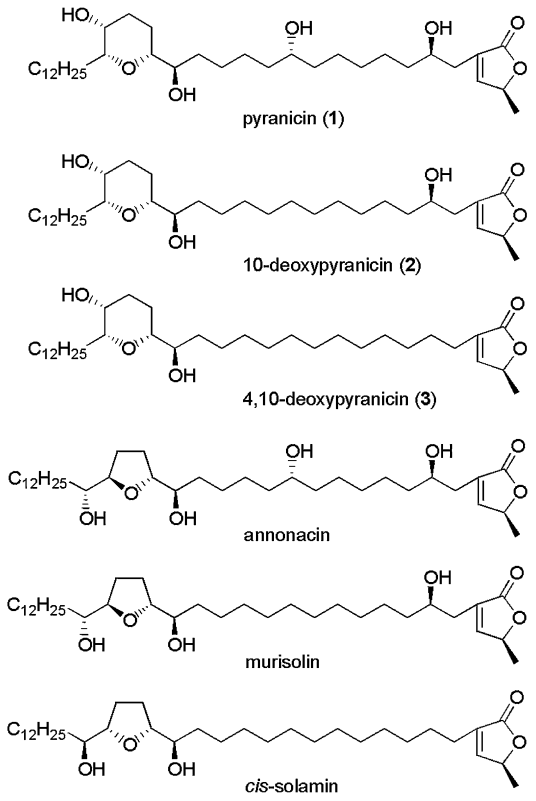


Figure 1. The structures of pyranicin (**1**) and its deoxygenated analogues, 10-deoxypyranicin (**2**), 4,10-dideoxypyranicin (**3**), and related mono-THF acetogenins, annonacin, murisolin, and *cis*-solamin.

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.

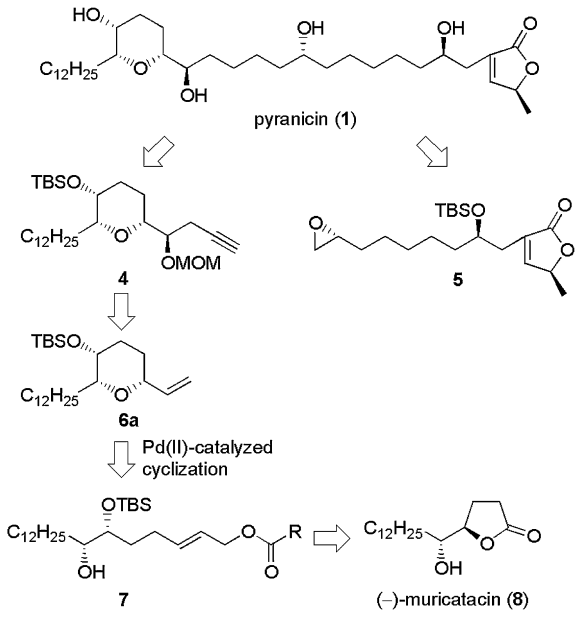
2. Results and discussion

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**