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Synthesis of solamin type mono-THF acetogenins using cross-metathesis

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ABSTRACT

The total synthesis of mono-THF acetogenins, *cis*-solamin A and B, and reticulatacin, was accomplished starting with muricatacin. The backbone of the mono-THF acetogenins was constructed by olefin cross-metathesis between the tetrahydrofuran moiety and γ-lactone moiety. An enzymatic kinetic transesterification procedure was successfully applied to the synthesis of an optically pure γ-lactone moiety. Notably, *cis*-THF compounds were obtained without using protective groups.

1. Introduction

Annonaceous acetogenins[1] exhibit a broad spectrum of biological activities including cytotoxic, antitumor, pesticidal, antifeedant, and immunosuppressive effects and contain either adjacent and non-adjacent tetrahydrofuran or tetrahydropyran rings and α,β-unsaturated γ-lactone rings. These compounds are thought to target the NADH-ubiquinone oxidoreductase (complex I) in mammalian and insect mitochondrial electron transport systems[2] and/or ubiquinone-linked NAD(P)H oxidase in cytoplasmic membranes of cancer cells.[3]

Their structural diversity and numerous biological properties have encouraged total synthesis.[4] We have already reported the stereoselective synthesis of acetogenins, such as solamin, murisolin, rollicosin, and pyranicin starting from muricatacin using a Sonogashira coupling reaction of the THF acetylene unit and butenolide vinyl iodide moiety as a key step.[1b] Curran,[5a] Tanaka,[5b] and Sinha[5c] were disclosed the synthesis of libraries of the THF moiety of acetogenins is important to search for drug discovery as a pioneer work. To obtain an acetogenin library for the evaluation of inhibitory activity against mitochondrial complex I, we have developed a simple route for the synthesis of mono-THF acetogenins in the course of our recent research regarding mitochondrial complex I inhibitors based on acetogenin structures. In the previous communication, we reported the total synthesis of *cis*-solamin A using a practical route containing no protection/deprotection steps.[6] Therefore, we selected the most simple mono-THF acetogenins, *cis*-solamin A (**1**) and B (**2**), and reticulatacin (**3**) as targets. *cis*-Solamin was isolated from the roots of *Annnona muricata* by Gleye et al. in 1998[7] (Fig. 1). The relative stereochemistry of the THF-diol part was determined to be *threo*–*cis*–*threo*, and the absolute structure of *cis*-solamin was expected to be either *cis*-solamin A (**1**) or *cis*-solamin B (**2**). Because of diverse biological activities and an unique biosynthetic mechanism, the total synthesis of *cis*-solamin was conducted by four groups, Stark's,[8] Donohoe's,[9] Brown's,[10] and Makabe's groups.[11] Synthetic *cis*-solamin A (**1**) and *cis*-solamin B (**2**) both showed remarkable inhibitory effects against mitochondrial complex I with an IC_{50} value of 2.2 and 2.1 nM, respectively.[11] In 2006, Hu et al. reported that natural *cis*-solamin is a mixture of two tetra-epimeric diastereoisomers consisting of *cis*-solamin A (**1**) and *cis*-solamin B (**2**).[12] Reticulatacin (**3**) was isolated from *Annnona reticulata* by McLaughlin in 1990.[13] The relative stereochemistry of the THF-diol part was determined to be *threo*–*trans*–*threo*, and it has a weak inhibitory effect (IC_{50}=20 nM).[14]

We herein report the synthesis of three stereoisomers of the THF unit and transesterification of butenolide using a cross metathesis reaction to obtain *cis*-solamin A (**1**) and B (**2**), and reticulatacin (**3**).

2. Results and discussion

Our method centers on the construction of the mono-THF segment via an olefin cross metathesis reaction[15,16] of the THF–allylic

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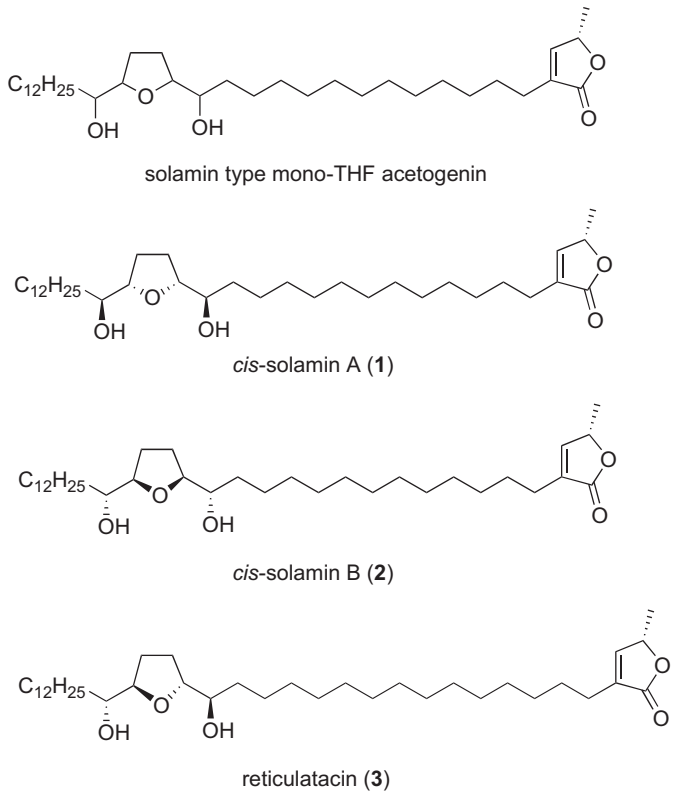
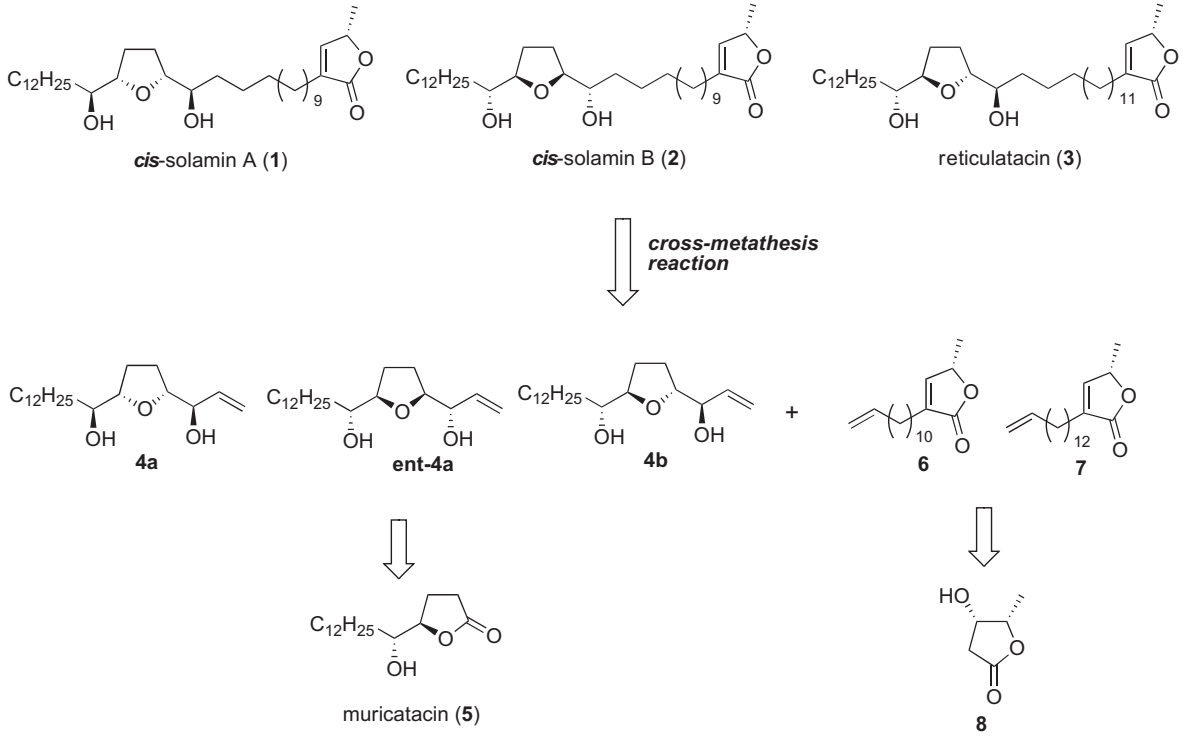


Figure 1. mono-THF acetogenins, *cis*-solamin A (**1**), B (**2**), and reticulatacin (**3**).

alcohol component and the γ-lactone moiety with the terminal double bond. Recently, Mootoo et al. applied the cross-metathesis strategy for a synthesis of mono-THF acetogenins.[17] An attractive aspect of this strategy is the convergent assembly of the mono-THF and lactone components. In view of the variety of natural and unnatural analogues available for the investigation of structure-activity relationships, this strategy can provide chemical libraries easily. For the metathesis reaction, an allylic alcohol **4** containing unprotected hydroxy groups is employed, and thus the alcohol **4** is prepared from a known compound, enantiopure muricatacin (**5**) checked by mosher method after recrystallization in hexane,[18] via Horner Emmons type olefination followed by an asymmetric dihydroxylation and Grignard reaction. The metathesis counterpart γ-lactone **6** or **7** is synthesized by the alkylation of an enantiopure hydroxy lactone **8**, which is prepared by an enzymatic kinetic transesterification[19] of the racemic lactone (±)-**8**. Since the racemic lactone (±)-**8** can be easily obtained by two-step reactions from commercially available *trans*-3-pentenenitrile, the enzymatic route can provide an optically pure lactone[20] with practical procedures (Scheme 1).

Synthesis of the THF–allylic alcohol **4a** is shown in Scheme 2. (−)-Muricatacin (**5**) was converted to a mesyl compound using $MsCl/Et_3N$ and the subsequent reduction with DIBAL-H in THF gave the hemi-acetal **10** in 57% yield in two steps. Horner Emmons type olefination and epoxidation of **10** using an excess of the lithium salt of diethyl allylphosphate gave an epoxy-*E*-diene **11** with a ratio of more than 20:1 (*E*/*Z*) in 64% overall yield as an inseparable mixture. Asymmetric dihydroxylation (AD-mix β)[21] of **11** and subsequent treatment with a catalytic amount of *p*-TsOH in CH_2Cl_2 afforded the desired THF–allylic alcohol **4a** as a major product in 52% yield with a minor regioisomer (26% yield). The diastereomeric excess of **4a** was determined to be >98%de. In addition, a enantiomer of **4a** was prepared from (+)-muricatacin (*ent*-**5**). Using this route, THF–allylic alcohol analogues varying in stereostructure could be similarly prepared with specific combinations of muricatacin analogues and asymmetric dihydroxylation reagents.

The α,β-unsaturated ester **13** starting from (−)-muricatacin (**5**) reported by us[22] was converted to **4b** and **4c** using cyclization with epoxide and oxidative degradation of the diol moiety to give the aldehyde **15** followed by a Grignard reaction in 55% yield for **16** and



Scheme 1. Synthetic plan for mono-THF acetogenins.