



Stereoselective synthesis of (±)-urechitol A employing [4+3] cycloaddition

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ABSTRACT

Urechitol A was synthesized as a racemate employing a [4+3] cycloaddition reaction and a methanol assisted intramolecular epoxide opening as key steps for efficient construction of the core tricyclic framework. The overall yield was 2.4% over 12 steps.

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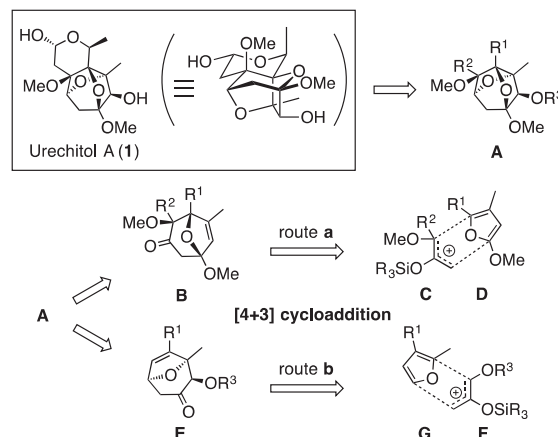
1. Introduction

Urechitol A (**1**) was isolated from the root extract of *Pentalinon andrieuxii*, which has been used commonly as a traditional medicine for cutaneous leishmaniasis in the Yucatan Peninsula, by Peña-Rodríguez's group in 2009.¹ This compound has a novel and unique structure including a highly functionalized cycloheptane ring with two oxygen bridges, and its relative configuration has been determined by X-ray crystal structural analysis. Biological activity of **1** itself has not been reported, however, our attention was focused on its unique 2,6-dioxatricyclo[3.3.1.0^{3,7}]nonane framework that is, dioxanalogue of noradamantane.² We have already published a rapid communication,³ in which we succeeded in the racemic synthesis of urechitol A employing a [4+3] cycloaddition reaction, and here, we wish to report a full account of our synthesis of (±)-urechitol A.

2. Results and discussion

Our synthetic strategy of urechitol A (**1**) is illustrated in Scheme 1. We decided to form the six-membered hemiacetal from an intermediate **A** at the later stage of the synthesis. In order to construct 2,6-dioxatricyclo[3.3.1.0^{3,7}]nonane **A**, we selected [4+3]

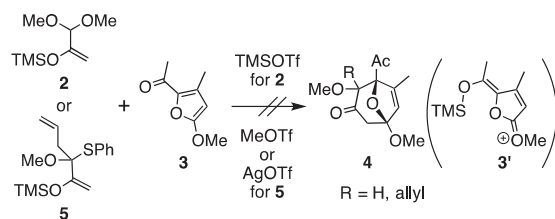
cycloaddition reaction between a furan and a silyloxyallyl cation substituted with a π -donating alkoxy group.^{2,4,5} Considering that there are two tetrahydrofuran rings in **A**, two types of [4+3] cycloaddition, **C**+**D** (route **a**) and **F**+**G** (route **b**), are possible. In both cases, cycloadducts **B** and **E** would be expected to possess oxygen functional groups and double bonds in the appropriate positions for further transformations into **1**. As described below, the route **a** resulted in failure, and total synthesis of urechitol A was achieved by employing route **b**.



Scheme 1. Structure of urechitol A (**1**) and synthetic strategies for **1**.

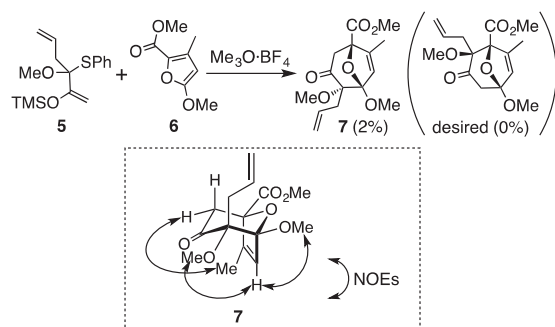
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At first, we examined [4+3] cycloaddition based on route **a**, by using acetylfuran **3**. Albizzati's group reported [4+3] cycloaddition reaction between dimethyl acetal **2** and simple furans in the presence of Lewis acid.⁴ We selected **2** as a model compound of siloxyallyl cation precursor, and their reaction conditions were applied to a cycloaddition to **3** (Scheme 2). The reaction ended up recovery of the furan **3**, the desired cycloadduct **4** was not obtained. It was thought that Lewis acid reacted with **3** to form **3'** before generation of the silyloxyallyl cation. Next we designed alternative cation precursor, mono-thioacetal **5**,^{6,7} which was thought to generate siloxyallyl cation in the presence of alkylating reagents or metal triflates. The reaction between furan **3** and mono-thioacetal **5**, however, resulted in undesired aldol reaction (MeOTf) or decomposition of the enol ether (AgOTf).



Scheme 2. [4+3] Cycloaddition of acetylfuran **3** based on route **a** (failed).

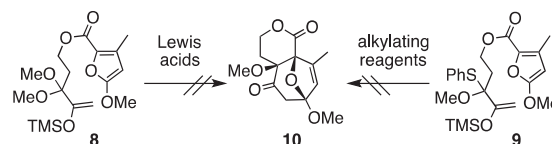
As the results of these reactions, the acetyl group of **3** was found to be problematic, and the furan unit was partially modified in order to suppress enolization. Cycloaddition between the mono-thioacetal **5** and the alternative furan unit, furoate **6**, was shown in Scheme 3. The [4+3] cycloaddition of **5** and **6** did proceed in the presence of Meerwein reagent, and oxabicyclo[3.2.1]octene skeleton **7** was obtained only in miserable yield, and unfortunately, the product **7** was found to have both undesired regio- and stereochemistry by NOESY experiment.



Scheme 3. [4+3] Cycloaddition of furoate **6** based on route **a**.

In the intermolecular [4+3] cycloaddition between **5** and **6** shown in Scheme 3, there were problems of miserable yield and undesired selectivity. In order to solve these problems, we also tried intramolecular [4+3] cycloaddition employing tethered substrates **8** and **9** (Scheme 4). Dimethyl acetal **8** was treated with several Lewis acids (TMSOTf, Sc(OTf)₃, Yb(OTf)₃ or TiCl₄), and mono-thioacetal **9** was treated with alkylating reagents (MeOTf or Me₃O·BF₃) under various conditions. However, only decomposition of **8** and **9** was observed in any case, and cycloadduct **10** was not obtained. Therefore, route **a** was abandoned here, and route **b** was adopted for the synthesis of urechitol A, as described below.

Our synthetic study of urechitol A based on route **b** was commenced also with the key [4+3] cycloaddition as shown in Table 1. The known compounds **11**⁸ and **12**⁴ were selected as the substrates for cycloaddition, and they were treated with several Lewis acids.⁵ As shown in entry 1, [4+3] cycloaddition between **11** and **12**



Scheme 4. Intramolecular [4+3] cycloaddition based on route **a** (failed).

Table 1
[4+3] Cycloaddition between **11** and **12** based on route **b**

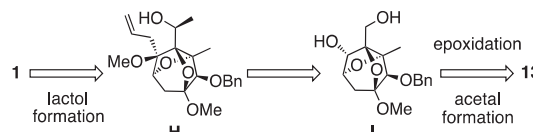
Entry	Lewis acid	Solvent	Conc.	Temp.	Yield
1	TMSOTf	CH ₂ Cl ₂	0.1 M	−78 °C	~10%
2	BF ₃ ·OEt ₂	CH ₂ Cl ₂	0.1 M	0 °C	~20%
3	TiCl ₄	CH ₂ Cl ₂	0.1 M	−78 °C	32%
4 ^a	TiCl ₄	CH ₂ Cl ₂	1.0 M	−78 °C	~30%
5	TiCl ₄	EtNO ₂	0.1 M	−78 °C	40%
6 ^b	TiCl ₄	EtNO ₂	0.1 M	−78 °C	46%

^a As an inseparable mixture with unidentified by-products.

^b NaHCO₃ (10 equiv) was used as an additive.

proceeded in the presence of TMSOTf to afford desired oxabicyclo[3.2.1]octene **13** as a sole regio- and stereoisomer in a low yield. The reaction yield was slightly improved by using BF₃·OEt₂ or TiCl₄ as a Lewis acid (entry 2 and 3), and the reaction in higher concentration resulted in a decrease in yield and a generation of unidentified by-products (entry 4). The use of nitroethane as a solvent afforded **13** in a moderate yield (entry 5), and finally, addition of sodium bicarbonate further improved the reaction yield to give **13** as a single isomer (entry 6).

Having succeeded in the key [4+3] cycloaddition, we proceeded to examine further transformation toward urechitol A. Synthetic plan of **1** from **13** is illustrated in Scheme 5. Tricyclic ether **1** would be obtained from **13** via epoxidation followed by acetal formation. After introduction of allyl and methyl groups, lactol moiety of **1** would be constructed via **H**.



Scheme 5. Synthetic plan of urechitol A (**1**) from cycloadduct **13**.

According to this plan, the allylic alcohol **13** was then oxidized into an unstable epoxy alcohol **14** under Sharpless conditions⁹ in the presence of sodium bicarbonate, which prevented the decomposition of the product during the reaction (Scheme 6). In absence of sodium bicarbonate, the yield decreased to 30%. The use of MCPBA resulted in exclusive Baeyer–Villiger oxidation instead of epoxidation.

Then we examined methanol assisted intramolecular epoxide opening in the presence of acid (Scheme 6). Treatment of the epoxide **14** with PPTS in methanol afforded trace amount of desired tricyclic ether **15** and methoxy ketone **16** (entry 1). On the other hand, treatment with TsOH·H₂O afforded desired **15** together with **16** in good yield as an inseparable mixture (**15**: **16** = 7: 3, entry 2). Similar result was obtained by treatment of the epoxide **14** with camphorsulfonic acid in dry methanol (entry 3). As the reaction proceeded even under anhydrous conditions like entry 3, it was

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