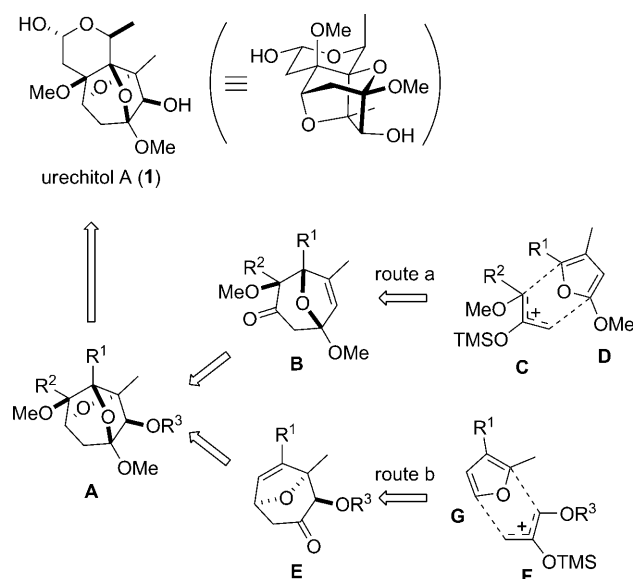


Stereoselective Total Synthesis of ($\pm$)-Urechitol A**

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Urechitol A (**1**) was isolated from the methanolic root extract of *Pentalinon andrieuxii* by Peña-Rodríguez and co-workers in 2009.^[1] *P. andrieuxii* is a plant used commonly in Yucatecan traditional medicine for the treatment of cutaneous eruptions derived from leishmaniasis, an infectious disease caused by protozoan parasites of the *Leishmania* genus. The relative stereochemistry of **1** has been elucidated unambiguously by X-ray crystallographic analysis (Scheme 1). This compound



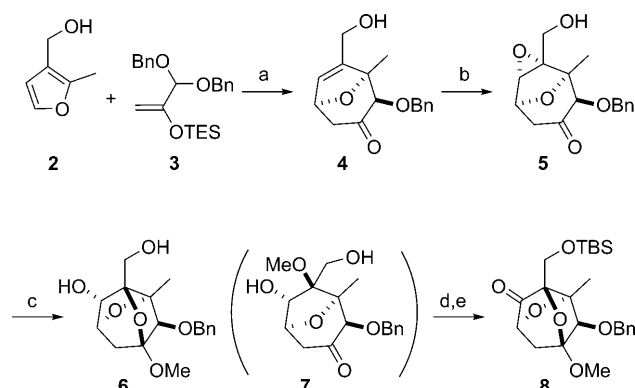
Scheme 1. Synthetic strategies for urechitol A (**1**). TMS = trimethylsilyl.

has a novel and very unique structure, incorporating a highly functionalized cycloheptane ring with two oxygen bridges. Although urechitol A itself exhibited no biological activity, its unique tetracyclic structure prompted us to investigate its synthesis.

Our synthetic strategy toward **1** is shown in Scheme 1. We decided to form the six-membered hemiacetal at a late stage

in the synthesis from **A**. For the construction of the seven-membered ring with the oxygen bridge (the so-called dioxo analogue of noradamantane^[2]), [4+3] cycloaddition between a furan and a silyloxyallyl cation with a π -donating alkoxy substituent was thought to be a straightforward approach.^[2,3] As there are two tetrahydrofuran rings in **A**, two types of cycloaddition are possible: **C** + **D** (route a) and **G** + **F** (route b). In both cycloadducts (**B** and **E**, respectively), the oxygen functionalities and double bonds were expected to be located in the required positions for further transformations leading to urechitol A. However, a preliminary investigation indicated that the cycloaddition between **C** (R^2 = allyl) and **D** (R^1 = CO₂Me) afforded a product with both undesired regio- and stereochemistry. Therefore, route b was adopted for the synthesis of urechitol A, as described below.

Our synthesis started from the key [4+3] cycloaddition reaction between known compounds **2**^[4] and **3**^[3b]; the product (**4**) was obtained as a sole regio- and stereoisomer in a moderate yield (Scheme 2). For the reaction, TiCl₄^[3a] was



Scheme 2. a) TiCl₄, EtNO₂, NaHCO₃, –78 °C, 46%; b) [VO(acac)₂], TBHP, NaHCO₃, CH₂Cl₂, RT, 47%; c) TsOH·H₂O, MeOH, 40 °C, 67% of **6** and 28% of **7**; d) TBSCl, imidazole, DMF, RT, 74%; e) TPAP, NMO, M.S. 4 Å, CH₂Cl₂, RT, quant. Bn = benzyl, TES = triethylsilyl, Et = ethyl, acac = acetylacetonate, TBHP = *tert*-butylhydroperoxide, Ts = *para*-toluenesulfonyl, Me = methyl, TBS = *tert*-butyldimethylsilyl, DMF = *N,N*-dimethylformamide, TPAP = tetra-*n*-propylammonium per-ruthenate, NMO = 4-methylmorpholine *N*-oxide, M.S. = molecular sieves.

used as a Lewis acid instead of the more generally used TMSOTf^[3b] and the reaction was carried out at a relatively lower concentration (0.1M) relative to that of the standard reaction conditions (1M)^[3b] to avoid the generation of unidentified by-products. The allylic alcohol was then oxidized into the unstable epoxy alcohol **5** under Sharpless conditions^[5] in the presence of NaHCO₃ as a basic additive, which prevented the decomposition of the product during the

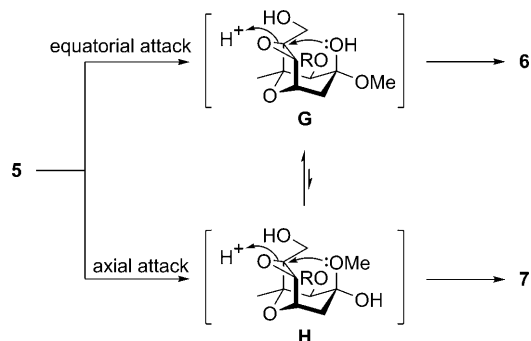
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reaction. Without NaHCO_3 , the yield decreased to 30 % and the use of *m*CPBA was found to be less effective.

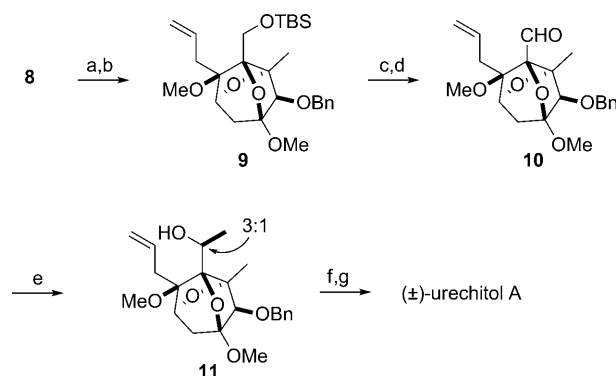
Acid treatment of **5** in methanol afforded desired tricyclic ether **6** and methoxy ketone **7** in 67 % and 28 % yields, respectively. As the reaction proceeded even under anhydrous conditions (camphorsulfonic acid in dry methanol), it was thought to have taken place by equatorial attack of methanol, mainly from the sterically less hindered *exo* face, and subsequent epoxide opening by the hydroxy group of the resulting hemiacetal **G** (Scheme 3). In contrast, epoxide



Scheme 3. Plausible mechanism of the epoxide opening.

opening with methanol to form **7** probably also occurred in an intramolecular manner via the diastereomeric hemiacetal intermediate **H**, which was generated by the axial attack of methanol or by isomerization (dehydration–hydration) of **G**. The primary alcohol of **6** was then protected as a TBS ether and the remaining secondary hydroxy group was oxidized into a ketone by TPAP^[6] to afford **8**, which readily absorbed water to form a hydrate. Therefore, **8** had to be dehydrated by heating with 4 Å molecular sieves in toluene at 80 °C before being used in the next reaction.

The ketone **8** was then treated with allylmagnesium bromide and a tertiary alcohol was obtained in 73 % yield along with 7 % of a separable diastereomer. After conversion into its methyl ether, the primary alcohol was liberated and oxidized to give aldehyde **10**, which underwent methylation with a Grignard reagent to afford secondary alcohol **11** as the major isomer. A lower temperature or the use of methyl-lithium afforded the same results. Finally, Lemieux–Johnson oxidation and subsequent debenzylolation afforded the crystalline (±)-urechitol A (**1**; m.p. 80–82 °C; Scheme 4).



Scheme 4. a) Allylmagnesium bromide, THF, 0 °C, 73 %; b) NaH, MeI, THF, 0 °C–RT, 87 %; c) TBAF, THF, RT, 92 %; d) TPAP, NMO, M.S. 4 Å, CH_2Cl_2 , RT, 92 %; e) MeMgCl, THF, 0 °C–RT, 67 % of **11** and 24 % of the stereoisomer; f) OsO_4 , NaIO₄, 2,6-lutidine, dioxane/ H_2O , RT, 67 %; g) H_2 , Pd(OH)₂, EtOH, RT, 87 %. THF = tetrahydrofuran, TBAF = tetra-*n*-butylammonium fluoride.

In summary, urechitol A (**1**) was synthesized as a racemate using a [4+3] cycloaddition reaction (**2** + **3** → **4**) and a methanol assisted intramolecular epoxide opening (**5** → **6**) as key steps for the efficient construction of the core tricyclic framework. The overall yield was 2.3 % over 12 steps. Synthesis of the optically active **1** for the determination of the absolute configuration is underway.

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