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First highly stereocontrolled synthesis of the unusual 1-hydroxy *endo*,*endo*-2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignan skeleton

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ABSTRACT

This Letter describes a highly diastereoselective synthesis of the unique 1-hydroxy *endo*,*endo*-2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton starting from a stereodefined 4-arylidenetetrahydrofuran obtained by a multicomponent reaction. The key step of this synthesis is a dealkylative cyclization reaction performed on the corresponding epoxide, generating four contiguous stereogenic centers with total stereocontrol.

Furofurans of type **1** having a 2,6-diaryl-3,7-dioxa-bicyclo[3.3.0]octane structure are a class of the lignan family of natural products that often exhibit interesting biological activities.[1] Among them, lignans **2** having a *tert*-hydroxy group at the 1-position are known to display powerful antioxidant properties[2] and insecticide-enhancing activity.[3] To our knowledge, until 2004, only three stereoisomers in this series of lignans such as **2a–d** were described in the literature that derived from the relative orientation between the C-1 hydroxyl group, and the electron-rich C-2 and C-6 aromatic substituents located on either the *exo* or *endo* face of the bicyclic core.[4] Recently, a new 1-hydroxy furofuran lignan that possesses significant antitubercular activity was isolated from *Valeriana laxiflora* and is characterized by an unusual stereochemistry. Indeed its structure was established as (+)-1-hydroxy-2,6-bis-*epi*-pinoresinol **2e** by spectroscopic methods and, to our knowledge, this natural product is the unique representative of this 1-hydroxyfurofuran series where the two aryl groups and the hydroxyl group are in a trans relative position (Fig. 1).[5]

Although numerous approaches have been developed for the synthesis of the furofuran series **1**,[6] only a few strategies have been published for the synthesis of this oxygenated subgroup[7] (**2**) and, none of these methods have been reported for the preparation of 1-hydroxy furofuran having the *endo–endo* stereochemistry. Having recently succeeded in the preparation of functionalized fused δ-hydroxy-γ-lactones of defined stereochemistry,[8] we reasoned that applying this method to the synthesis of 1-hydroxy furofuran lignan **2**, starting from (*Z*)-2-aryl-4-aryl-idenetetrahydrofuran readily prepared from a three-component reaction developed in our group,[9] would provide a useful method for the preparation of the *endo–endo* furofuran series. Indeed, we envisaged that the stereochemical outcome of the epoxidation reaction performed on these stereodefined 4-arylidenetetrahydrofurans **3** could be controlled by the steric bulk of the aryl group. A dealkylative cyclization reaction on the resulting epoxide **4** would deliver the diaxial tetrahydrofuranolactone **5**. A subsequent decarbalkoxylation followed by a reduction would provide the desired 1-hydroxy furofuran **2** having an unusual stereostructure (Scheme 1).

To investigate this new synthetic approach, (*Z*)-2-phenyl-4-benzylidenetetrahydrofuran **3a** was chosen as the model substrate. Treatment of **3a** with 3 equiv of MCPBA in CH_2Cl_2 at room temperature afforded epoxy-diester **4a** in 97% yield. As expected, epoxidation took place selectively from the less-hindered side of furan and only one diastereoisomer was detected in the ^1H NMR spectrum of the crude product. The dealkylative cyclization reaction was performed using 0.2 equiv of *p*-toluenesulphonic acid (PTSA) in CH_2Cl_2 at room temperature. The only detectable diastereoisomer, the diaxial tetrahydrofuranolactone ester **5a** was isolated in 87% yield (Scheme 2). Its structure was unambiguously established by X-ray crystallography which clearly confirmed the relative stereochemistry at positions 1, 2, 5, and 6 of the furanolactone ester (Fig. 2).[10]

The decarbalkoxylation was next examined. Treatment of **5a** under Krapcho's conditions[11] using 5 equiv LiCl, afforded the expected furanolactone **6a** in only 27% yield after 3 days at

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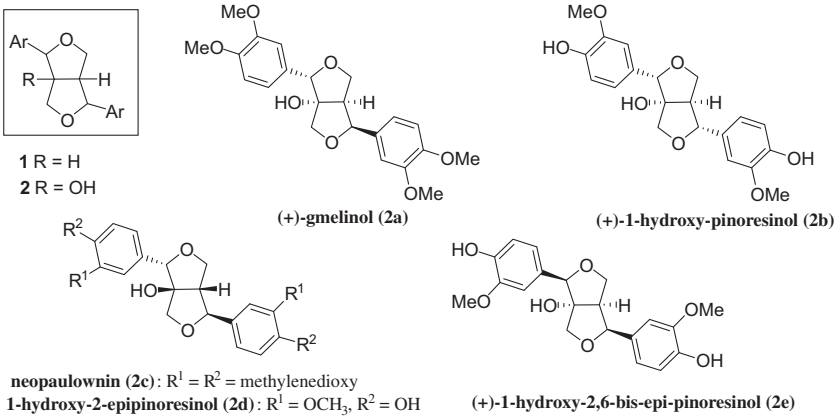
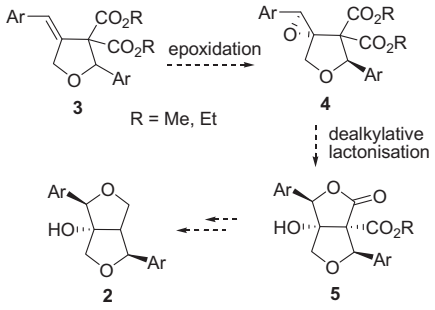
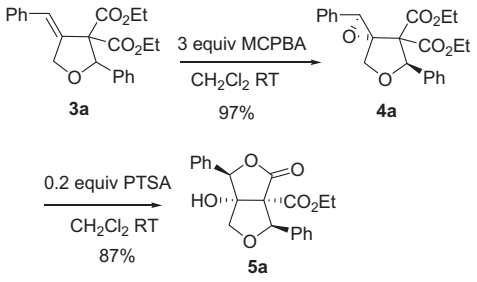


Figure 1. Stereostructure of representative 1-hydroxyfurofuran lignans.



Scheme 1. Envisaged strategy for the synthesis of diaxial tetrahydrofuranolactone esters **5**.



Scheme 2. Preparation of the diaxial tetrahydrofuranolactone **5a**.

130 °C in DMSO. To enhance this process and shorten the long reaction times, the same decarbalkoxylation was performed under microwave irradiation and the results are summarized in Table 1. When the reaction was conducted at 200 °C in various solvents, the expected product was isolated in modest yields (35–47%) due to product decomposition (entries 2–4). By decreasing the temperature to 180 °C, furanolactone **6a** was isolated in 56% yield as a single isomer (entry 5).

Conversion of lactone **6a** into the corresponding tetrahydrofuran derivative **2f** via formation of the lactol intermediate or ring-opening reaction was carried out following established procedures.[12] However, preparation of hydroxy furofuran **2f** via lactol intermediate **7a** proved to be difficult. Indeed, several attempts using diisobutyl aluminium hydride (DIBAH) to reduce lactone **6a** resulted in either no reaction or a mixture of inseparable triol **8a**, lactol **7a,** and recovered lactone **6a**. A more satisfactory result was obtained for this reduction when using 2 equiv of $LiAlH_4$ in THF at room temperature which furnished the expected lactol **7a**

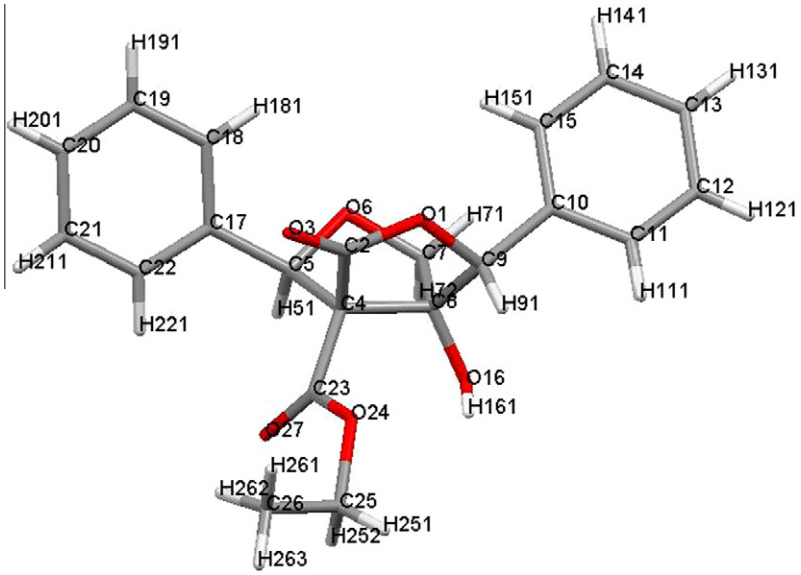


Figure 2. X-ray analysis of **5a**.