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Total synthesis of (+)-xyloketal D, a secondary metabolite from the mangrove fungus *Xylaria* sp.

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Abstract—(+)-Xyloketal D was prepared in a one-pot multistep domino reaction by heating optically active 5-hydroxy-4-methyl-3-methylenepentan-2-one (*R*) in toluene with 2,4-dihydroxyacetophenone. The absolute configuration of the natural product was confirmed by preparation of the starting enone from a lactone of established absolute configuration.

The xyloketals are a group of secondary metabolites, which were recently isolated from the mangrove fungus *Xylaria* sp.[1] Xyloketal A **1** has not only attracted attention because of its unusual C_3-symmetric structure,[2] but is also of interest as a potent inhibitor of acetylcholine esterase. The absolute configuration of **1** and another representative, xyloketal D **2**, was elucidated by using quantum mechanical calculations of their CD spectra and by comparison with the experimental data (Fig. 1).[1]

We now report on the first total synthesis of enantiomerically pure xyloketal D **2**. In this synthesis, two building blocks are condensed in a single operation, comprising several consecutive chemical transformations. The absolute configuration, previously determined theoretically, could also be confirmed by comparison of the optical rotations.

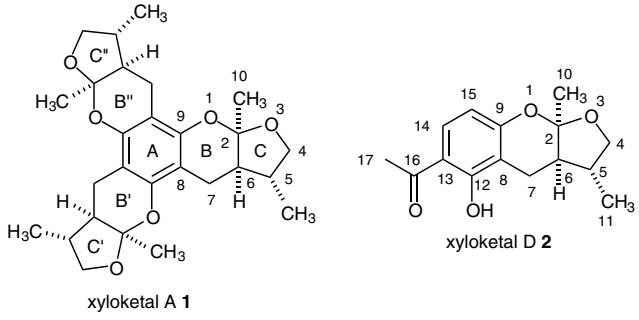
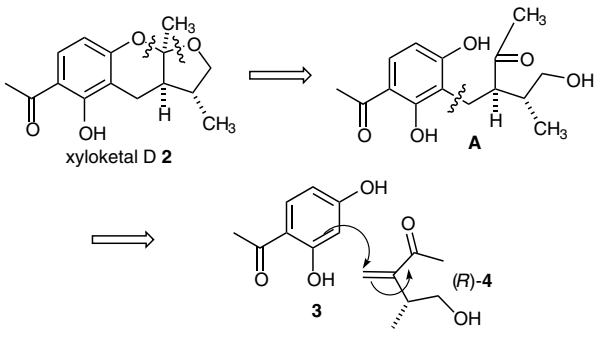


Figure 1. Structures of xyloketal A **1** and D **2**.

In our retrosynthetic scheme, we intended to perform a Michael addition of 2,4-dihydroxyacetophenone **3** to the enantiomerically pure enone (*R*)-**4** to yield the intermediate **A**, followed by spontaneous ketal formation to give the natural product **2** (Scheme 1). However, there are a number of questions connected with this simple synthetic plan, which can only be answered by the experimental evidence. Michael additions of electron-rich phenols with acrylic acids are known in connection with coumarin syntheses,[3] but the reactions of enones with less electron-rich acetophenones are not so common.[4] Furthermore, the site of addition (C-3 or C-5)



Scheme 1. Retrosynthetic analysis of xyloketal D **2**.

Keywords: Xyloketal D; Total synthesis; Ketal formation; Marine secondary metabolites.
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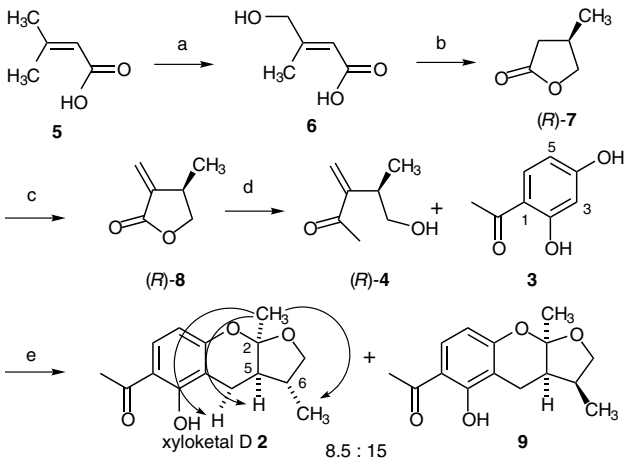

Scheme 2. Synthesis of the two isomeric xyloketals **2** and **9** by condensation of the building blocks (*R*)-**4** and **3**: (a) SeO_2 (45%); (b) (i) Ru-catalyst/H_2 (Ref. 5) (100%, 93% ee), (ii) H^+ (74.5%); (c) (i) HCOOEt, NaH; (ii) CH_2O; (d) MeLi (54% for c and d); (e) 110 °C, toluene, 5 h (81%).

and the relative orientation of the methyl groups in the two newly generated chiral centers is uncertain.

In order to verify the result of the determination of the absolute configuration of **2**,[1] we had to start with a compound of known absolute configuration. An ideal precursor presented itself in the form of the methylbutyrolactone (*R*)-**7**, prepared by Noyori and co-workers[5] via enantioselective hydrogenation of the substituted acrylic acid **6**[6] using a chiral ruthenium–BINAP catalyst, followed by acid-catalyzed cyclization to (*R*)-**7** (93% ee) (Scheme 2, procedure for (*R*)-**4a**).[8] The introduction of the methylene group to yield the α-methylenebutyrolactone (*R*)-**8** was achieved in good yield in a two-step sequence by reaction with ethyl formate and formaldehyde.[7] In the subsequent conversion of lactone (*R*)-**8** to the methyl ketone, a two-fold addition of methyllithium could be reduced to a minimum by lowering the reaction temperature to −30 °C. Also, a conjugate addition of the 'hard' methyllithium nucleophile to (*R*)-**8** was not observed and the open-chain enone (*R*)-**4** was isolated in 73% yield. The subsequent condensation of the two building blocks (*R*)-**4** and **3** was achieved by simply heating the components in toluene without any addition of catalysts. Evidently, the acidity of the phenols was sufficient for an autocatalytic process. In addition to the main product **2** with the all-*cis* configuration, the *anti*-isomer **9** was isolated as a minor by-product (ratio **2**:**9** = 8.5:1.5). Small amounts of the theoretically possible C-5 adduct of acetophenone **3** were isolated in model studies.[9]

The *cis*-junction of the pyran and furan rings was secured by NOE experiments, irradiating the relevant protons as shown in structure **2** (Scheme 2). In addition, the *cis*-junction was further confirmed by X-ray analysis of related model compounds.[9]

The isomers **2** and **9** could be separated by crystallization. The spectral data of the synthetic product were identical to those of the natural product **2**, including the absolute configuration, thus confirming the quantum-mechanically determined absolute configuration as shown in **2**.

Acknowledgements

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References and Notes

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