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Total Synthesis of (–)-Xyloketal A

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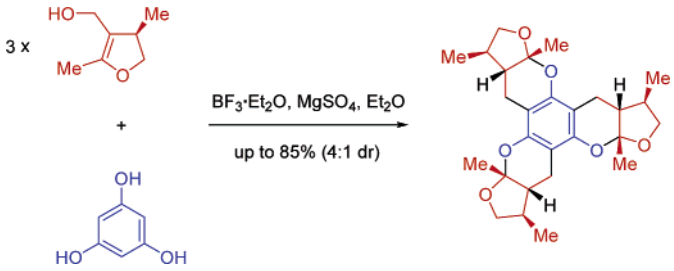
ABSTRACT



The first total synthesis of the C_3-symmetric and biologically active natural product, (–)-xyloketal A, has been accomplished in one step from phloroglucinol (1,3,5-trihydroxybenzene) and (4*R*)-3-hydroxymethyl-2,4-dimethyl-4,5-dihydrofuran. This remarkably direct process involved an exceedingly facile and diastereoselective boron trifluoride diethyl etherate-promoted triple electrophilic aromatic substitution reaction that was coupled to three bicyclic acetal formation reactions.

The isolation and structural characterization of seven closely related natural products, the xyloketals, from a mangrove fungus of the *Xylaria* species have been reported recently in a series of papers by Lin and co-workers.[1−3] Of these natural products, (−)-xyloketal A (**1**) has a unique and aesthetically pleasing C_3-symmetric molecular structure that was elucidated by detailed spectroscopic studies and by X-ray crystallography (Figure 1).[1] In the solid state, it was revealed that this substance adopts a symmetric bowl-shaped conformation that is presumably reinforced by anomeric effects. The absolute stereochemistry of this novel secondary metabolite was assigned by interpretation of the CD spectrum.[1] (−)-Xyloketal A (**1**) has also been shown to be a potent inhibitor of acetylcholine esterase and to have L-calcium channel blocking activity.[1,2] Thus, (−)-xyloketal A (**1**) represents an important lead compound for the treatment of cardio- and cerebrovascular conditions as well as neurological diseases.[1,2] In view of the structure and biological properties of this particular substance, we have been actively engaged in studies toward the total synthesis of the xyloketal natural products.[4,5] In this Letter, we report the first total synthesis of (−)-xyloketal A (**1**).[6]

It was realized, before the outset of our earlier synthetic studies,[4,5] that (−)-xyloketal A (**1**) could be prepared by a triple electrophilic aromatic substitution reaction of phloroglucinol (1,3,5-trihydroxybenzene) **2** and the reactive intermediate **4** (Figure 1). The product of these initial electrophilic substitution processes would then be expected to react, under appropriate acidic conditions, to afford the thermodynami-

(1) Lin, Y.; Wu, X.; Feng, S.; Jiang, G.; Luo, J.; Zhou, S.; Vrijmoed, L. L. P.; Jones, E. B. G.; Krohn, K.; Steingröver, K.; Zsila, F. *J. Org. Chem.* **2001**, *66*, 6252.

(2) Wu, X. Y.; Liu, X. H.; Lin, Y. C.; Luo, J. H.; She, Z. G.; Houjin, L.; Chan, W. L.; Antus, S.; Kurtan, T.; Elsässer, B.; Krohn, K. *Eur. J. Org. Chem.* **2005**, 4061.

(3) Wu, X.; Liu, X.; Jiang, G.; Lin, Y.; Chan, W.; Vrijmoed, L. L. P. *Chem. Nat. Compd.* **2005**, *41*, 27.

(4) We have previously reported a racemic synthesis of the two possible diastereoisomers of a tris-demethyl analogue of xyloketal A and a racemic synthesis of a demethyl analogue of xyloketal D. We have also reported the first total synthesis of (±)-xyloketal D which is, in a structural sense, one of the simpler members of this family of natural products, see: (a) Pettigrew, J. D.; Bexrud, J. A.; Freeman, R. P.; Wilson, P. D. *Heterocycles* **2004**, *62*, 445. We have also described an asymmetric total synthesis of (−)-xyloketal D and its enantiomer, see: (b) Pettigrew, J. D.; Freeman, R. P.; Wilson, P. D. *Can. J. Chem.* **2004**, *82*, 1640. These syntheses featured the cycloaddition reactions of appropriately functionalized *o*-quinone methides and dihydrofurans as a key step. The further application of this chemistry, to complete the total synthesis of xyloketal A (**1**), has not been successful.

(5) We have recently described an alternative approach to the synthesis of the xyloketal A (**1**) based on a novel phenylboronic acid-mediated triple condensation reaction of α,β-unsaturated aldehydes and phloroglucinol, see: Pettigrew, J. D.; Cadieux, J. A.; So, S. S. S.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 467.

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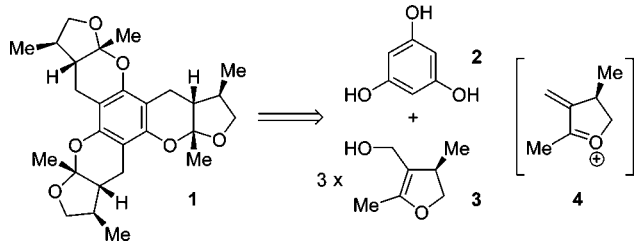


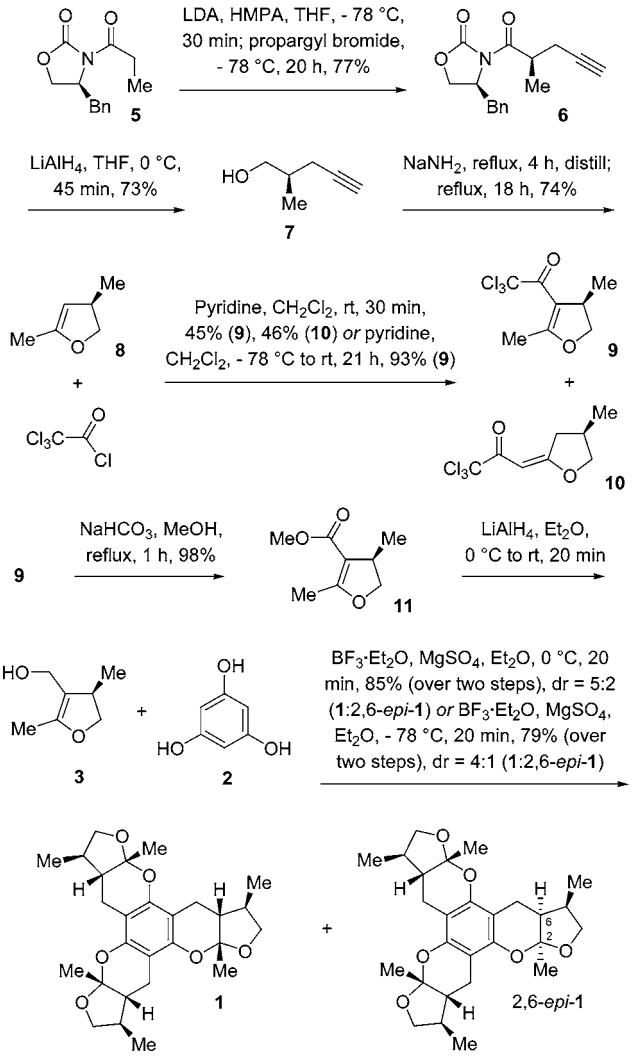
Figure 1. Molecular structure and retrosynthetic analysis of xyloketal A.

cally stable cis-fused bicyclic acetal moieties of the natural product. It was also appreciated that the stereochemistry of the acetal formation reactions would be directed by the steric influence of the stereogenic C4-methyl substituent of the reactive intermediate **4**. In principle, this reactive intermediate could be generated on ionization of the corresponding chiral nonracemic alcohol **3**.[7] To demonstrate this synthetic objective, a method was developed for the preparation of a precursor to the chiral nonracemic alcohol **3**. Thus, the methyl ester **11** was prepared from the known oxazolidinone **5** (Scheme 1).[8]

Deprotonation of the oxazolidinone **5** in a mixture of tetrahydrohydrofuran and hexamethylphosphoramide (HMPA, ~10%) with lithium diisopropylamide (LDA, 1.5 equiv), and on subsequent reaction with propargyl bromide (4 equiv) at −78 °C for 20 h, afforded the oxazolidinone **6** in good yield (77%) and as a single diastereoisomer.[9] This oxazolidinone was then reduced with lithium aluminum hydride to afford the known chiral nonracemic alcohol **7**.[10,11] This acetylenic alcohol was in turn converted to the known *endo*-cyclic dihydrofuran **8** on heating with a substoichiometric amount of sodium amide followed by thermal isomerization of the corresponding *exo*-cyclic dihydrofuran.[4b,12]

To prepare the required methyl ester **11**, the dihydrofuran **8** was reacted (based on literature procedures) with trichloroacetyl chloride and pyridine.[13,14] This afforded a readily separable mixture of the desired trichloroketone **9** (45% yield) and a substantial quantity of the regioisomeric trichloroketone **10** (46% yield).[15] Presumably, the latter compound was formed via isomerization of the *endo*-cyclic dihydrofuran **8** to the corresponding *exo*-cyclic dihydrofuran under the reaction conditions. To suppress the formation of the regioisomeric trichloroketone **10**, the reaction was repeated at −78 °C. This resulted in the isolation of the trichloroketone **9** in very good yield (93%). Subsequent methanolysis of the trichloroketone **9** afforded the methyl ester **11** in excellent

Scheme 1. Total Synthesis of (−)-Xyloketal A



(6) Krohn and co-workers have attempted the synthesis of xyloketal A (**1**) from racemic 5-hydroxy-4-methyl-3-methylenepentan-2-one and phloroglucinol. In this instance, the desired tris-adducts were isolated in 6% yield as a mixture of eight diastereoisomers, see: (a) Krohn, K.; Riaz, M.; Flörke, U. *Eur. J. Org. Chem.* **2004**, 1261. In this paper, an asymmetric synthesis of (−)-xyloketal D via a conjugate addition reaction of 2,4-dihydroxyacetophenone to the (4*R*)-enantiomer of the aforementioned ketone was also described. In addition, Krohn and co-workers reported the synthesis of demethyl analogues of the xyloketal natural products in this paper. For a preliminary communication of this work, see: (b) Krohn, K.; Riaz, M. *Tetrahedron Lett.* **2004**, *45*, 293.

(7) We have established, in simplified model systems, that this novel triple electrophilic aromatic substitution reaction and subsequent bicyclic acetal formation process can be promoted with a variety of acidic reagents in the presence of anhydrous magnesium sulfate, see: Pettigrew, J. D.; Wilson, P. D. *J. Org. Chem.* **2006**, *71*, 1620.

(8) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.

(9) For reports on the use of HMPA in alkylation reactions of derivatives of oxazolidinone chiral auxiliaries, see: (a) Fadel, A. *Tetrahedron: Asymmetry* **1994**, *5*, 531. (b) Versteeg, M.; Bezuidenhoudt, B. C. B.; Ferreira, D.; Swart, K. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1317. (c) Versteeg, M.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron* **1999**, *55*, 3365.

(10) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(11) For an alternative synthesis (employing a resolution procedure) and proof of absolute stereochemistry of the chiral nonracemic alcohol **7**, see ref 4b.

(12) The final reaction product was contaminated with a small amount of the corresponding *exo*-cyclic dihydrofuran (<7%).

(13) (a) Hojo, M.; Masuda, R.; Sakaguchi, S.; Takagawa, M. *Synthesis* **1986**, 1016. (b) Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, 483.

(14) A direct one-step procedure for the synthesis of dihydrofuran esters from the corresponding dihydrofurans has been reported, see: Stetter, H.; Lorenz, G. *Chem. Ber.* **1985**, *118*, 1115. However, in our hands, a complex mixture of reaction products was obtained when the dihydrofuran **8** was employed as a reaction substrate.

(15) The trichloroketone **10** was isolated as a single geometrical isomer. The geometry of the double bond was not determined but it is reasonable to assume, based on electronic and steric considerations, that it is trans.

yield.[16] In preliminary experiments, it was found that the methyl ester **11** could be cleanly reduced to the required alcohol **3** with lithium aluminum hydride. However, the latter compound was found to be somewhat unstable to isolation and purification and so it was used directly in subsequent experiments. Thus, according to preliminary model studies, a mixture of a two-fold excess (per phenolic reaction site of phloroglucinol **2**) of the alcohol **3** and phloroglucinol **2** (1 equiv) in ether at 0 °C was stirred with boron trifluoride diethyl etherate (1 equiv) and anhydrous magnesium sulfate.[7] Within 20 min, an exceptionally clean synthetic transformation occurred that led to the isolation of a chromatographically inseparable mixture of xyloketal A (**1**) and 2,6-*epi*-xyloketal A (2,6-*epi*-**1**) in 85% yield (dr = 5:2).[17,18] Although the diastereoselectivity of the overall process was not exceptional, the diastereoselectivity of each of the three individual ring formation reactions was certainly respectable (dr = ~9:1). Moreover, the ^{1}H NMR spectrum of the crude reaction mixture was dominated by signals that corresponded to the C_3-symmetric natural product.[1] To improve the overall diastereoselectivity of this remarkable process, the above reaction was repeated at −78 °C.[19] This led to the isolation of a mixture of xyloketal A (**1**) and 2,6-*epi*-xyloketal A (2,6-*epi*-**1**) in similar yield (79% yield). However, the diastereoselectivity of the overall process was significantly increased (dr = 4:1). In this case, the diastereoselectivity of each of the three individual ring formation reactions had reached an impressive level (dr = ~19:1). An analytically pure sample of synthetic (−)-xyloketal A (**1**) was subsequently obtained on crystallization from petroleum ether. The ^{1}H and ^{13}C NMR spectra of this material were identical with those recorded for the natural product.[1] Moreover, the optical rotation (in both sense and magnitude) as well as the melting point of the synthetic material were in close agreement with those reported in the original isolation paper.[1] Thus, the absolute stereochemistry of the natural product is now firmly established.

In conclusion, the first total synthesis of (−)-xyloketal A (**1**) has been accomplished from phloroglucinol **2** and the chiral nonracemic alcohol **3**. The key step of this total synthesis involved an exceedingly facile and diastereoselective boron trifluoride diethyl etherate-promoted triple electrophilic aromatic substitution reaction that was coupled to three bicyclic acetal formation reactions. An efficient five-step asymmetric synthesis of (4*R*)-methyl-2,4-dimethyl-4,5-dihydrofuran-3-carboxylate (**11**), the direct precursor of alcohol **3**, was also developed from the readily available oxazolidinone **5**. The application of this potentially biomimetic synthetic method toward the total synthesis of the remaining members of the xyloketal family of natural products will be reported in due course.

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Supporting Information Available: General experimental details, experimental procedures, and full product characterization data for all of the compounds synthesized, as well as ^{1}H and ^{13}C NMR spectra for compounds **6**, **9**−**11**, **1**, and 2,6-*epi*-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For a related procedure, see: de Buyck, L.; de Pooter, H.; Schamp, N. *Bull. Soc. Chim. Belg.* **1988**, *97*, 371.

(17) Herein, the numbering scheme is based on that described by Lin and co-workers (see ref 1).

(18) The stereochemistry of the single minor diastereoisomer from this reaction was tentatively assigned as to that of the 2,6-epimer of xyloketal A. In addition, the diastereomeric ratio of the products from this reaction was determined by integration of the partially resolved signals in the downfield region of the crude ^{1}H NMR spectrum.

(19) The reaction was also repeated at 0 °C with 4 equiv of the alcohol **3**. In this instance, a mixture of xyloketal A (**1**) and 2,6-*epi*-xyloketal A (2,6-*epi*-**1**) was isolated in 14% yield (dr = 5:2). In addition, no evidence for the formation of mono- or bis-addition products was recorded. This reflects the relative instability of the alcohol **3** and the increased reactivity of the more electron-rich mono- and bis-addition products toward electrophilic aromatic substitution processes.