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A Catalytic Enantioselective Total Synthesis of (−)-Wodeshiol

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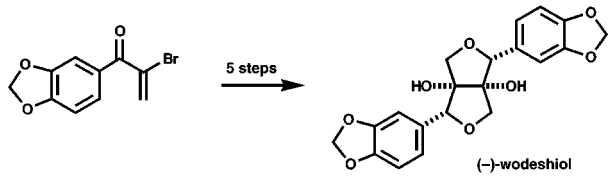
ABSTRACT



(−)-Wodeshiol of >99% ee has been synthesized from the α,β-enone shown using a number of noteworthy steps including a novel C−C coupling reaction.

The lignan class of natural products consists of a large structurally diverse group of molecules which are all biosynthesized in chiral form from the achiral precursor coniferyl alcohol, (*E*)-3′-methoxy-4′-hydroxycinnamyl alcohol, by remarkable sequences of oxidation dimerization and cyclization events. Most of the reported chemical syntheses of lignans either lead to racemic compounds or utilize chiral starting materials, e.g., sugars.[1] Described herein is a short, stereocontrolled and enantioselective synthesis of (−)-wodeshiol (**1**),[2] (also known as kigeliol[2c]) a member of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane subclass of lignans, using a chiral oxazaborolidine for catalytic control of absolute configuration. This synthesis also demonstrates the utility of a novel C−C bond-forming homocoupling reaction employing bimetallic catalysis.

The starting point in the synthesis of **1** was 3,4-methylenedioxybenzaldehyde (piperonal) which was converted to vinyl ketone **2** by sequential reaction with vinyllithium (THF, −78 °C, 30 min, 97%) and activated MnO_2 (CH_2Cl_2, 0 °C, 30 min, 75%). Ketone **2** was transformed in one flask into the α-bromo derivative **3** by α,β-addition of Br_2 followed by Et_3N-promoted elimination of HBr under the conditions indicated in Scheme 1. Enantioselective reduction of **3** by catecholborane with the (*R*)-proline derived B-methyl CBS catalyst[3] provided the allylic bromo alcohol **4**[4] (88% ee, 84% yield) which was subjected to Br−Li exchange and stannylation to give the corresponding tributyltin compound **5** (84%).

The next step in the synthesis of **1** utilized a newly developed coupling reaction of 1-substituted vinyltri-*n*-butylstannanes to form 2,3-disubstituted 1,3-butadienes.[5−7] When **5** was heated with 10 mol % of $Pd(PPh_3)_4$, 5 equiv of CuCl, and 2 equiv of $CuCl_2$ in DMSO at 60 °C for 2 h, the desired coupled 1,3-diene **6** was obtained in 99.2% ee and 82% yield after silica gel chromatography.[8] Hydroxyl-assisted

(1) For recent reviews see: (a) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75. (b) Ward, R. S. *Tetrahedron* **1990**, *46*, 5029.

(2) (a) Anjaneyulu, A. S. R.; Ramaiah, P. A.; Row, L. R.; Venkateswarlu, R.; Pelter, A.; Ward, R. S. *Tetrahedron* **1981**, *37*, 3641. (b) Pelter, A.; Ward, R. S.; Venkateswarlu, R.; Kamakshi, C. *Tetrahedron* **1992**, *48*, 7209. (c) Inoue, K.; Inouye, H.; Chen, C.-C. *Phytochemistry* **1981**, *20*, 2271.

(3) For a recent review on this catalytic enantioselective method, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986.

(4) The (*R*)-enantiomer **4** can be predicted to predominate in this product on the basis of extensive earlier results and the mechanistic model.[3]

(5) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

(6) For a related Cu(I)-promoted dimerization of β-Me_3Sn-substituted α,β-unsaturated carbonyl compounds, see: (a) Piers, E.; McEachern, E. J.; Romero, M. A. *Tetrahedron Lett.* **1996**, *37*, 1173. (b) Piers, E.; McEachern, E. J.; Romero, M. A.; Gladstone, P. L. *Can. J. Chem.* **1997**, *75*, 694. (c) Piers, E.; Gladstone, P. L.; Yee, J. G. K.; McEachern, E. J. *Tetrahedron* **1998**, *54*, 10609.

(7) Pd(II)-promoted homocoupling reactions of vinylstannanes have also been reported; see: (a) Alcaraz, L.; Taylor, R. J. K. *Synlett* **1997**, 791. (b) Kang, S.-K.; Namkoong, E.-Y.; Yamaguchi, T. *Synth. Commun.* **1997**, *27*, 641. (c) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905.

(8) A minor amount (∼10%) of the meso isomer of **6** was also present.

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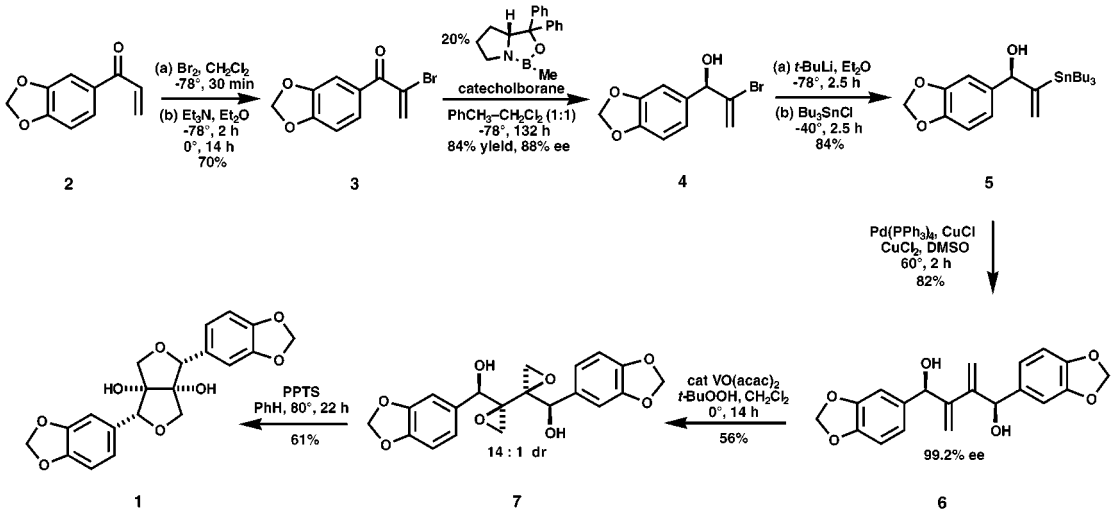
Scheme 1



bis-epoxidation[9,10] of **6** gave after silica gel chromatography the desired diol **7** (along with a minor diastereomer; 14:1 diastereoselection) using *t*-BuOOH as oxidant and $VO(acac)_2$ as catalyst at 0 °C. Mild acid treatment of **7** (2.2 equiv of pyridinium tosylate in benzene at 80 °C) produced (−)-wodeshiol in 61% yield: mp 152−153 °C (lit.[2] mp 153−154 °C); $[\alpha]^{23}_D$ −11.7 (*c* 0.7, $CHCl_3$) (lit.[2] $[\alpha]_D = -12$ in $CHCl_3$); HRMS (FAB) $[M + Na]^+$, *m/z* 409.0899, calcd 409.0879. The ^1H and ^{13}C NMR data obtained for synthetic **1** agreed well with those reported[2] for natural wodeshiol. Finally, a single-crystal X-ray diffraction analysis of synthetic **1** unambiguously confirmed the structure as shown in Figure 1.[11]

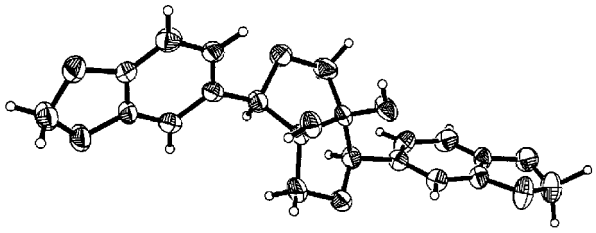


Figure 1. ORTEP structure of wodeshiol as determined by X-ray diffraction.

The synthesis of wodeshiol reported herein fully confirms the previous assignment of structure **1**[2] to this interesting and highly functionalized lignan. It also supports the previously assumed[2] absolute configuration (as shown in structure **1**) since the highly enantioselective CBS reduction of **3** would be expected on the basis of much prior knowledge[3] to produce the absolute configuration shown in **4**. This successful first synthesis of **1** illustrates the value of the bimetallic homocoupling reaction which has recently been developed.[5] Finally, it is coincidental but of interest that the present synthesis and the biosynthetic pathway of wodeshiol involve as the sole carbon source a starting material having the carbon skeleton Ar−C−C−C.

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Supporting Information Available: Full experimental procedures for the synthesis of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991151D

(9) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(10) Bailey, M.; Markó, I. E.; Ollis, W. D. *Tetrahedron Lett.* **1991**, *32*, 2687.

(11) (a) X-ray data (0.71073 Å, 213(2) K) for synthetic wodeshiol: $C_{20}H_{18}O_8$, orthorhombic; $P2_12_12_1$; $a = 9.2575(3)$ Å, $b = 17.7010(5)$ Å, $c = 20.765(2)$ Å, $\alpha = \beta = \gamma = 90°$; $Z = 8$; R1[$I > 2\sigma(I)$] = 0.0540, wR2 = 0.0703; GOF on $F^2 = 0.916$. (b) Detailed X-ray diffraction data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.