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Diastereoselective Radical Cyclization of Bromoacetals: Efficient Synthesis of (±)-Botryodiplodin

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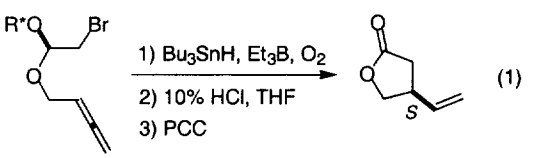
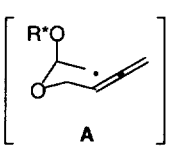
Abstract: A stereoselective synthesis of (±)-botryodiplodin is presented. The key reaction is a radical cyclization of a bromoacetal (Ueno-Stork reaction). The stereogenic acetal center has been used to control the stereoselectivity of the process: the difficulty in controlling the stereochemistry at C(3) of the tetrahydrofuran moiety during the cyclization step has been overcome by a double one-pot reduction procedure starting from a *gem*-dibromide. © 1999 Elsevier Science Ltd. All rights reserved.

Recently, we have shown that the radical cyclization of haloacetals (Ueno-Stork reaction)[1-5] is highly stereoselective relative to the acetal center.[6] High stereoselectivities have been observed for the formation of 4-substituted tetrahydrofurans. Preparation of optically pure β-substituted γ-butyrolactones by use of an easily removable chiral auxiliary was reported (eq. 1). A model taking into account an anomeric effect has been proposed to rationalize the stereochemical outcome.[6,7]

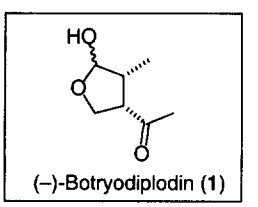


(1)



A

R* = (1*R*, 2*S*)-2-phenylcyclohexyl



(–)-Botryodiplodin (**1**)

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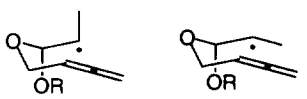
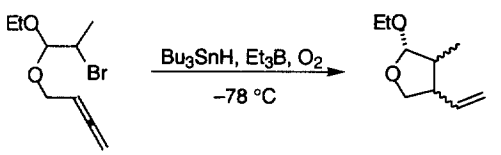
In this account, we describe a short, efficient and stereocontrolled synthesis of (±)-botryodiplodin (**1**) which can be easily adapted for the synthesis of enantiomerically pure material. (−)-Botryodiplodin (**1**) is a simple lactol natural product which has been isolated from *Botryodiplodia theobromae* and *Penicillium roqueforti*.[8-10] This mycotoxin exhibits antibiotic and antileukemic activity.[11] Its relative and absolute configuration has been determined by total synthesis.[12-19] However, despite a strong interest for its preparation, only two syntheses of enantiomerically pure botryodiplodin have been reported,[15,17] both of them using chiral building block derived from natural products (*D*-ribose and methylenomycin A).

Based on our stereochemical model for the Ueno-Stork reaction, preparation of 3,4-disubstituted tetrahydrofurans was expected to be problematic: the C(4) center should be nicely controlled by the acetal center (model **A**), however, the C(3) center should not be easy to control because of the opposite effects of the two vicinal substituents. Indeed, according to the classical Beckwith-Houk model,[20,21] the alkoxy group should favor the *trans* product (model **B**) and the C(4) substituent should favor the *cis* product (model **B'**). The control of the stereochemistry at C(3) has to be solved in order to be able to synthesize botryodiplodin by this method. The first attempts to control the stereochemistry at C(3) gave as expected *cis*/*trans* mixtures.[6] This was confirmed with **2**, a potential precursor of botryodiplodin. Treatment of **2** under standard cyclization conditions (Bu_3SnH, Et_3B, O_2 at −78 °C) gave **3** as mixture of three isomers.

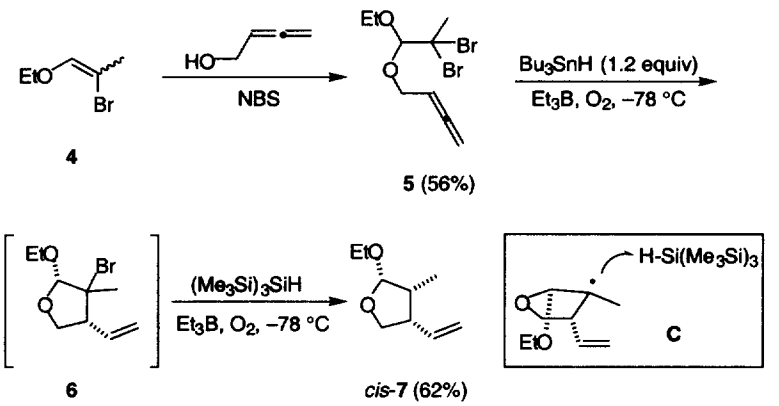


B (→ *trans*) **B'** (→ *cis*)

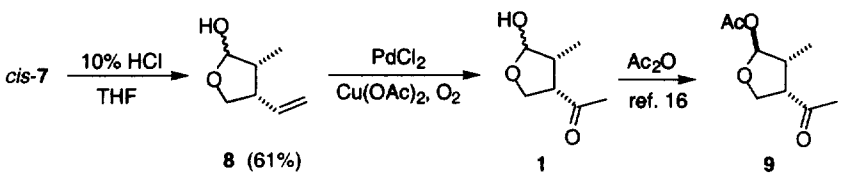


2 **3** (mixture of isomers)

In order to solve this stereoselectivity problem, the *gem*-dibromide **5** was prepared from enol ether **4** and 2,3-butadien-1-ol by treatment with *N*-bromosuccinimide. Radical cyclization with one equivalent of tin hydride furnished the intermediate bromotetrahydrofuran **6** (mixture of two isomers). Without isolation of bromide **6**, a second equivalent of tin hydride was added to the reaction mixture and the desired reduced acetal *cis*-**7** was isolated together with *trans*-**7** product (*cis*-**7**/*trans*-**7** 2:1). A better stereocontrol was obtained when a bulkier reducing agent such as tris(trimethylsilyl)silane[22] was used for the second reduction step. In this way, the desired product *cis*-**7** was obtained in 62% yield in a one-pot procedure starting from **5**.[23] Traces of organotin derivatives were removed by treatment of the reaction mixture with an aqueous NaOH solution.[24] Careful analysis of the crude product revealed that *trans*-**7** was also present (*cis*-**7**/*trans*-**7** 4:1) together with 2% of non-identified isomers. The preferential formation of *cis*-**7** is easily explained by reduction of the cyclic radical from the less hindered face *anti* to the two vicinal substituents (model **C**).



The synthesis of racemic botryodiplodin was achieved by hydrolysis of the acetal **7** (10% HCl) followed by Wacker oxidation of the lactol **8** using a recently reported procedure ($PdCl_2/Cu(OAc)_2/O_2$).[25] Under these mild conditions, the unstable botryodiplodin **1** was obtained as a mixture of anomers. Physical and spectral data are in accordance with literature data.[16] For further characterization, the lactol was transformed to the known botryodiplodin acetate **9**.[16]



In conclusion, we have demonstrated that bromoacetal radical cyclizations controlled by the acetal center can be used for the stereoselective preparation of 3,4-*cis*-disubstituted tetrahydrofurans such as botryodiplodin. Preliminary experiments with a chiral enol ether derived from *trans*-2-phenylcyclohexanol indicates that our approach can be applied for the preparation of enantiomerically pure botryodiplodin. This last point as well as further applications of this method for the synthesis of natural products will be reported in a forthcoming full paper.

Acknowledgments. This work was supported by the "Fonds National Suisse de la Recherche Scientifique".

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[23] Experimental procedure for the cyclization of **5** to **7**: A soln. of the dibromoacetal **5** (1.43 g, 4.56 mmol) and Bu_3SnH (1.57 g, 5.4 mmol) in toluene (100 ml) was cooled at –78 °C and a 1M soln. of Et_3B in hexane (6.4 ml, 6.4 mmol) was added followed by air (4.0 ml). The soln. was kept at –78 °C for 3 h. Then $(TMS)_3SiH$ (1.34 g, 5.4 mmol) was added followed by air (4.0 ml). The resulting soln. was kept at –78 °C for 3 h. A 1M NaOH soln. (60ml) was added and the heterogeneous mixture was stirred for 2 h at rt. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography (pentane/Et_2O) to afford *cis*-**7** (0.44 g, 62%) as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.96 (*dt*, *J* = 17.1, 10.1, C*H*=CH_2); 4.98-4.90 (*m*, H-C(2), CH_2=CH); 4.06 (*t*, *J* = 7.6, 1 H, H-C(5)); 3.77-3.68 (*m*, 2 H, H-C(5), C*H*HCH_3); 3.45-3.38 (*m*, CH*H*CH_3); 2.77 (*ddd*, *J* = 17.0, 9.3, 4.3, H-C(4)); 2.38-2.10 (*m*, H-C(3)); 1.18 (*t*, *J* = 7.1, C$H_3$$CH_2$); 0.91 (*d*, *J* = 7.2, CH_3). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 139.6 (*d*), 115.4 (*t*), 104.9 (*d*), 72.1 (*t*), 62.7 (*t*), 46.1 (*d*), 41.2 (*d*), 15.3 (*q*), 9.7(*q*). IR (film): 3076, 2976, 2881, 1639, 1428, 1078, 1043, 912.

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