Asymmetric Synthesis of Tetrasubstituted Tetrahydrofuran, 2-Epigoniothalesdiol, Employing Stereoselective Hydrogenation

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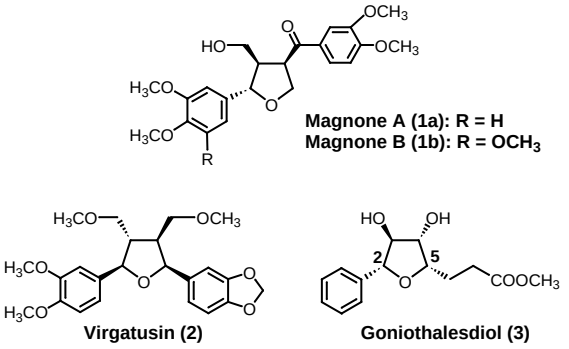
Abstract: An efficient and stereodefined process is described for the preparation of a 3,4-dihydroxy-2,5-disubstituted tetrahydrofuran ring with the contiguous stereogenic centers and the asymmetric synthesis of 2-epigoniothalesdiol is also reported by featuring the elaboration of the functionalized homochiral lactone derived from C_2-imide.

Key words: goniothalesdiol, tetrasubstituted tetrahydrofuran, stereoselective deoxygenation, hemiketal, trisubstituted γ-lactone



Figure

Tetrahydrofuran backbone is among the most common heterocyclic units found in natural products and structurally complex ones feature in many biologically potent compounds such as pheromones,[1] polyether antibiotics,[2] and marine epoxylipids.[3] Due to their interesting activity as well as unique structural characteristics, they have been the subject of an extensive synthetic effort which has culminated in numerous syntheses.[4] Noteworthy members among this class of compounds are optically active tetrahydrofuran derivatives with tri- and tetrasubstituents serving as good templates for the construction of pharmacologically important furanoid groups and exhibiting various degrees of potency and specificity (Figure).[5] In this connection we have also recently reported a novel and stereoselective conversion of lactones to polysubstituted cyclic ethers[6a] employing nucleophilic addition of Grignard reagents in the presence of $CeCl_3$ followed by the Lewis acid-induced deoxygenation and the first total synthesis of tetrasubstituted tetrahydrofuran, (-)-virgatusin (**2**).[6b] Stereochemical outcome obtained from the deoxygenation reaction using trisubstituted lactones with α,β-dibenzyloxymethyl and γ-aryl substituents evidently depends on the γ-substituent.[6]

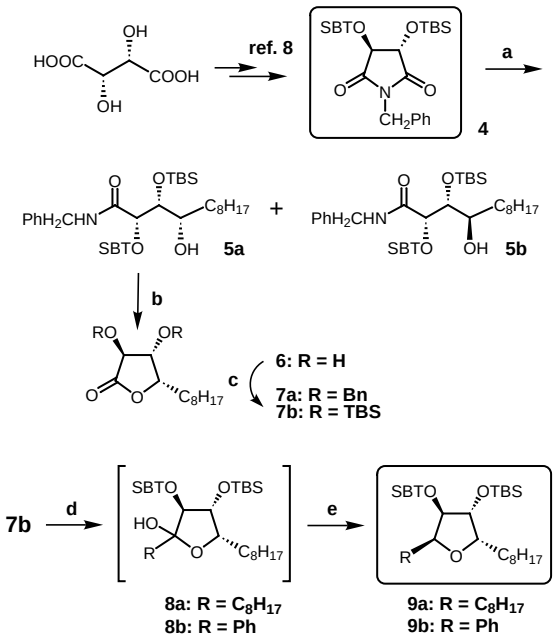
On the other hand, another type of dihydroxlated tetrahydrofuran, goniothalesdiol (**3**), was isolated in 1998 from the bark of the Malaysian tree *Goniothalamus borneensis* (Annonaceae). This was revealed to have significant cytotoxicity against P388 mouse leukemia cells and insecticidal activities,[5c] and a new addition to the styryl-type lactone series.[7] Taking advantage of these successive reactions of nucleophilic addition and stereoselective hydrogenation of its ketal derivative, we wish to communicate our synthetic efforts for the 3,4-dihydroxy-2,5-disubstituted tetrahydrofuran, such as goniothalesdiol (**3**), from C_2-imide.

In formulating the synthetic plan for **3**, we recognized that the absolute configurations at C(3) and C(4) are the same as the configurations at the corresponding C(2) and C(3) of D-tartaric acid. Further we envisioned that the stereogenic center of C(5) could originate from the nucleophilic addition to the C_2-imide obtained from D-tartaric acid followed by reduction based on our previous reports.[8] The remaining C(2) stereogenic center of **3** would have to be independently set in an asymmetric hydrogenation according to the strategy mentioned above.

As shown in Scheme 1, *N*-benzyl-C_2-imide **4** obtained from D-tartaric acid was treated with octylmagnesium bromide followed by reduction of the α-hydroxylactam intermediate with $NaBH_4$, leading to the corresponding hydroxyamide **5a** in 67% yield with exclusive stereoselectivity.[8] Accompanying formation of the other stereoisomer **5b** was observed in mere trace amounts after isolation using silica gel column chromatography. Then, **5a** was cyclized under acidic conditions to give the dihydroxylactone **6**. Whereas the use of BnBr-Ag_2O for the protection of the dihydroxyl functions in **6** brought about unsatisfactory racemization at C-5 in **7a**, the reaction with TBSCl-imidazole in DMF provided the disilylated compound **7b** as a single isomer (determined by ^{13}C NMR) in almost quantitative yield.

Next, we investigated the direct conversion of **7b** to the corresponding substituted tetrahydrofuran via Lewis acid-induced reductive deoxygenation. Thus, **7b** was subjected to reaction with the second Grignard reagents (alkyl- and arylmagnesium bromide) at -78 °C in the presence of $CeCl_3$ as reported previously,[6] followed by BF_3•OEt_2-promoted hydrogenation with Et_3SiH[9] of the hemiketal intermediates **8** at the same temperature. The reactions in both

cases proceeded within 10 minutes to afford the deoxygenated tetrasubstituted furans **9a** and **9b**, respectively, in good yields with complete stereoselectivity (determined by ^{13}C NMR and HPLC analysis). No other stereoisomer or ring-opened diol type product resulting from the attack of excess

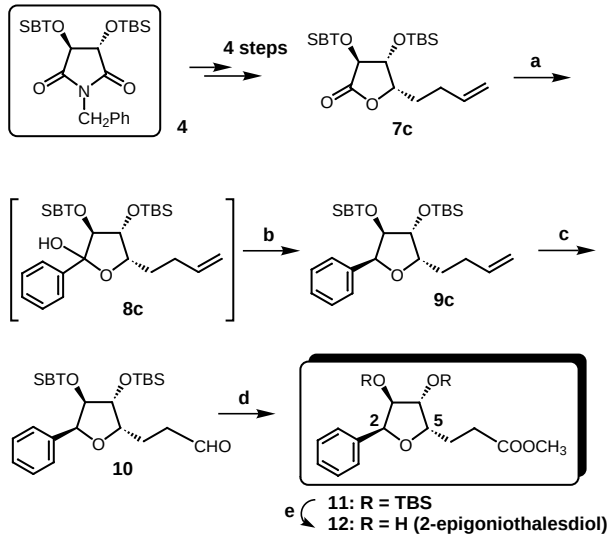


Reagents and conditions: (**a**) 1. $C_8H_{17}MgBr$, THF, 0 ºC; 2, $NaBH_4$, EtOH; 67% (**5a**) (2 steps); trace (**5b**) (2 steps) ; (**b**) 10% HCl-dioxane (1 : 1), 80 ºC; 95%; (**c**) BnBr-Ag_2O, CH_3COOEt; 51% (**7a**); TBSCl, imidazole, DMF; 97% (**7b**); (**d**) 1. $C_8H_{17}MgBr$, $CeCl_3$, THF, -78 ºC (**8a**); PhMgBr, $CeCl_3$, THF, -78 ºC (**8b**); 2. Et_3SiH, BF_3•OEt_2, CH_2Cl_2, -78 ºC; 64% (**9a**) (2 steps); 66% (**9b**) (2 steps).

Scheme 1

Grignard reagent to **7b** was observed. Stereochemistry of the new asymmetric center in **9a** was unambiguously determined to be *S*, since it possesses a C_2-axis of symmetry. **9b** was also estimated to have the same configuration based on the similarity of its spectral data. In contrast to our previous reports,[6] it could proceed through the exclusive attack of Et_3SiH to the oxocarbenium ion intermediate from the opposite site of the α-OTBS group independent of the γ-substituent. Presumably a manifestation of productlike steric destabilization of the transition state leading to the *cis* 2,3-stereochemistry is being observed.[9a]

With above stereochemical outcome in hand, we turned our attention to the asymmetric synthesis of 2-epigoniothalesdiol since the preparation of unnatural epimers and other structural analogs of styryllactone groups has generated much interest. This is based on the fact that the biological activity of these molecules varies substantially with the number, position and stereochemistry of the functional groups into the furan skeleton. As summarized in Scheme 2, the homochiral lactone **7c**, $[\alpha]_D^{30}$ -62.2° (c 1.45, EtOH), with a butenyl side chain was easily and stereoselectively prepared according to the above method in an enantiomerically pure form from **4** in 65% yield (4 steps). Treatment of **7c** with phenylmagnesium bromide at -78 °C in the presence of $CeCl_3$ furnished the labile hemiketal intermediate **8c**, which was readily effected by BF_3•OEt_2-induced deoxygenation with Et_3SiH at the same temperature with care (the use of excess Et_3SiH partially hydrogenated the olefinic part in **8c** as well as the deoxygenation reaction of the hemiketal skeleton), to lead cleanly to the tetrasubstituted furan **9c**, $[\alpha]_D^{28}$+46.0° (c 1.05, EtOH), also as a sole stereoisomer (determined by ^{13}C NMR) in 91% yield. Then, the double bond in **9c** was cleaved via dihydroxylation with OsO_4 to the aldehyde **10**. This was successively oxidized with bromine in MeOH[10] to the methyl ester **11**, $[\alpha]_D^{30}$+36.9° (c 0.57, EtOH), in 83% yield, followed by final deprotection of the silyl groups to complete the total synthesis of (+)-2-epigoniothalesdiol (**12**),[11] $[\alpha]_D^{29}$+66.6° (c 0.74, EtOH), in 37% overall yield from C_2-imide **4**.



Reagents and conditions: (**a**) PhMgBr, $CeCl_3$, THF, -78 ºC; (**b**) Et_3SiH, BF_3•OEt_2, CH_2Cl_2, -78 ºC; 91% (2 steps); (**c**) 1. OsO_4, NMO, acetone-H_2O (1 : 1); 99%; 2. $NaIO_4$, Et_2O-H_2O (1 : 1); (**d**) Br_2, $NaHCO_3$, MeOH-H_2O (9 : 1); 83% (2 steps); (**e**) cat. *p*-TsOH, MeOH; 77%.

Scheme 2

In summary, this work constitutes the first asymmetric synthesis of 2-epigoniothalesdiol from D-tartaric acid based on the stereoselective Lewis acid-promoted hydrogenation, and verifies the structure proposed in the literature for this natural product, since no report concerning the total synthesis of goniothalesdiol has been appeared to date.

Acknowledgement

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(11) ^{1}H and ^{13}C NMR data ($CDCl_3$) for **12**. ^{1}H NMR δ 1.26 (2H, 2O*H*, bs), 2.04 (2H, td, *J* = 6.8, 6.8 Hz), 2.44-2.64 (2H, m), 3.69 (3H, s), 3.98-4.39 (3H, m), 5.31 (1H, C2-*H*, d, *J* = 3.3 Hz), 7.34 (5H, s). ^{13}C NMR δ 23.5, 30.5, 51.8, 76.9, 79.1, 81.3, 82.2, 126.6, 127.8, 128.6, 136.7, 174.9.

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