JOC*Note*

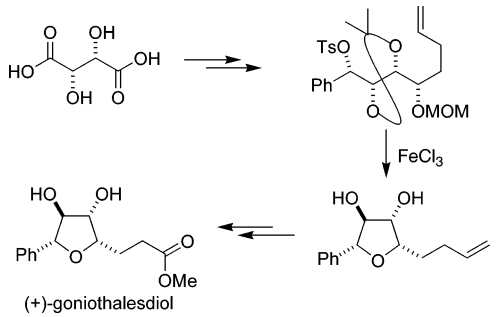
Stereoselective Synthesis of (+)-Goniothalesdiol

Kavirayani R. Prasad* and Shivajirao L. Gholap

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

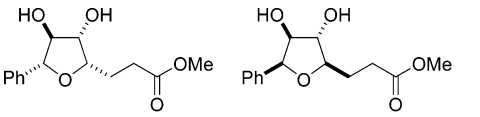
prasad@orgchem.iisc.ernet.in

Received January 24, 2006

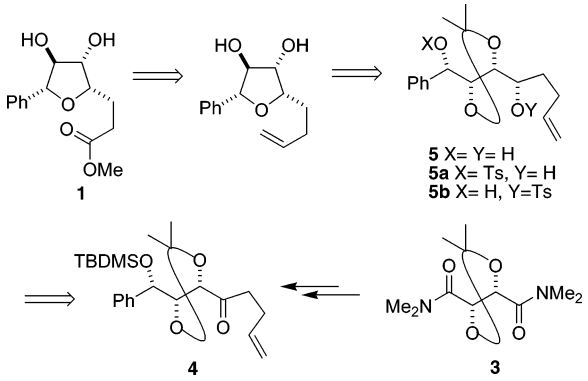


Stereoselective synthesis of antitumor tetrahydrofuran (+)-goniothalesdiol was achieved in high overall yield from (−)-D-tartaric acid. Key features include an $FeCl_3$ mediated THF formation with very high selectivity. Synthesis of natural gonithalesdiol and its analogue 2,5-bis-*epi*-goniothalesdiol was achieved from a common intermediate.

The tetrahydrofuran backbone is a ubiquitous heterocyclic unit found in a number of biologically active natural products such as *Annonaceae* acetogenins[1] and polyether antibiotics.[2] Goniothalesdiol (**1**), isolated from the bark of the Malaysian tree *Goniothalamus borneensis*, is another type of tetrahydrofuran having a 3,4-dihydroxy 2,5-dialkyl substitution.[3] The widespread antitumor activity commonly exhibited by the styryllactones is also associated with this compound and is found to show promising activity against P388 mouse leukemia cells.[4]



SCHEME 1. Retrosynthesis for Goniothalesdiol



Four syntheses of this bioactive tetrahydrofuran have been reported, and a formal approach has also been disclosed. A chiron approach starting from D-glucuronolactone[5] and D-mannitol[6] were disclosed by Yoda et al. and Babjak et. al. However, both these methods employ either a lengthy reaction sequence (16 steps from glucuronolactone for the unnatural goniothalesdiol) or a nonstereoselective process from mannitol, which involves the separation of diastereomers. The elaboration of *anti*-aldol adducts from erythrulose was the key step in the approach for the formal synthesis of goniothalesdiol by Murga et al.[7] Sharpless catalytic asymmetric epoxidation and Sharpless asymmetric dihydroxylation reactions were utilized in the recent synthesis reported by Yadav et. al., starting from cinnamyl alcohol.[8] More recently, Carreno et. al. have reported the synthesis starting from tartaric acid ester, involving a sulfoxide strategy pioneered by Solladie.[9]

Our approach to the synthesis of goniothalesdiol **1** was based on an intramolecular stereospecific cyclization of the hydroxy tosylate **5a** of 1,4-diol **5** (Scheme 1). It was envisaged to synthesize the required hydroxy tosylate **5a** from the silyloxyketone **4**, which can easily be obtained from tartaric acid. It was also visualized that altering the sequence of intramolecular ether formation, that is, the regioselective cyclization of the hydroxy tosylate **5b** would lead to the synthesis of goniothalesdiol analogue **2**.

The synthetic sequence was started with the silyloxyketone **4**, which was readily obtained from the bisdimethylamide of tartaric acid **3**, employing a combination of selective Grignard additions and a stereoselective reduction.[10] Reduction of ketone **4** with L-selectride produced the alcohol **6** with very high selectivity.[11] Alcohol **6** was protected as its methoxy methyl

* Corresponding author. Fax: +918023600529.

(1) (a) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rev.* **2005**, *22*, 269. (b) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. (c) Cave, A.; Figadere, B.; Laurens, A.; Cortes, D. Acetogenins from Annonaceae. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Eds; Springer-Verlag: New York, 1997; Vol. 70, pp 81−288.

(2) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407.

(3) Cao, S.-G.; Wu, X.-H.; Sim, K.-Y.; Tan, B. K. H.; Pereira, J. T.; Goh, S.-H. *Tetrahedron* **1998**, *54*, 2143.

(4) For a review on the cytotoxic activity and other bioactivity of styryllactones: (a) Mereyala, H. B.; Joe, M. *Curr. Med. Chem: Anti-Cancer Agents* **2001**, *1*, 293. (b) Blàzquez, M. A.; Bermejo, A.; Zafra-Polo, M. C.; Cortes, D. *Phytochem. Anal.* **1999**, *10*, 161.

(5) (a) Yoda, H.; Nakaseko, Y.; Takabe, K. *Synlett* **2002**, 1532. (b) For a synthesis of 2-*epi*-goniothalesdiol, see: Yoda, H.; Simojo, T.; Takabe, K. *Synlett* **1999**, 1969.

(6) (a) Babjak, M.; Kapitan, P.; Gracza, T. *Tetrahedron Lett.* **2002**, *43*, 6983. (b) Babjak, M.; Kapitan, P.; Gracza, T. *Tetrahedron* **2005**, *61*, 2471.

(7) Murga, J.; Ruiz, P.; Falomir, E.; Carda, M.; Peris, G.; Marco, J.-A. *J. Org. Chem.* **2004**, *69*, 1987.

(8) Yadav, J. S.; Raju, A. K.; Rao, P. P.; Rajaiah, G. *Tetrahedron: Asymmetry* **2005**, *16*, 3283.

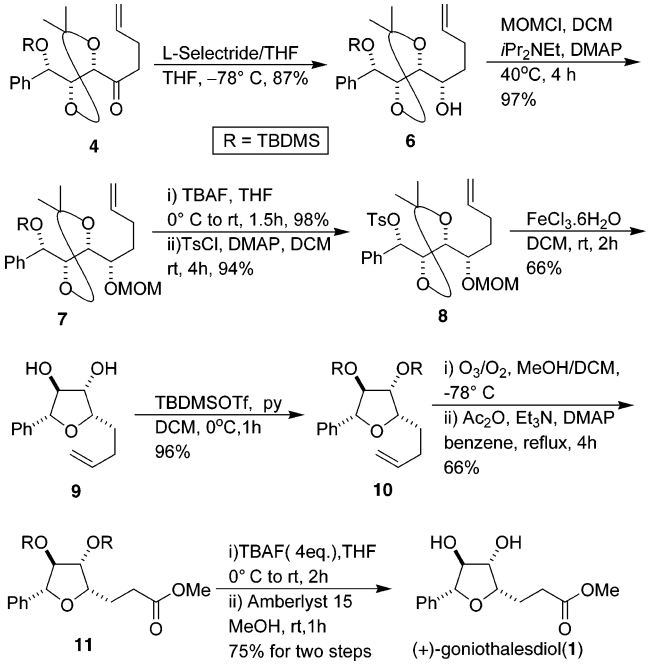
(9) Carreno, M. C.; Hernandez-Torres, G.; Urbano, A.; Colobert, F. *Org. Lett.* **2005**, *7*, 5517.

(10) Prasad, K. R.; Gholap. S. L. *Synlett* **2005**, 2260.

(11) The formation of other diastereomers was not observed within detectable limits in the ^1H NMR spectrum. Reduction with reducing agents such as $NaBH_4$ and DIBAL-H was not selective and produced diastereomeric alcohols in varying ratios.

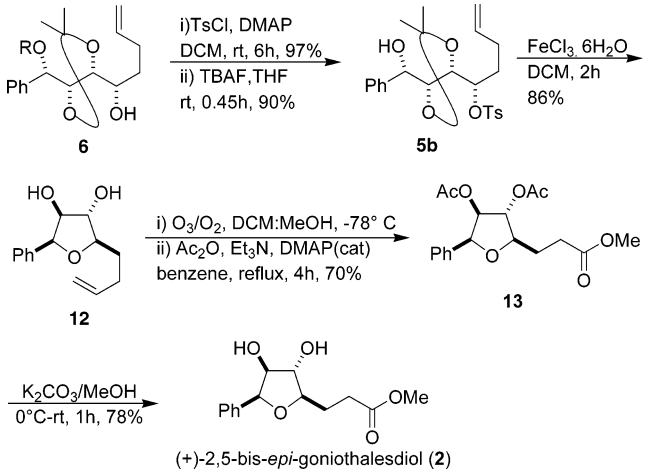
10.1021/jo060159f CCC: $33.50
Published on Web 03/30/2006

SCHEME 2. Stereoselective Synthesis of (+)-Goniothalesdiol



ether (MOM) **7** with chloromethoxy methyl ether in the presence of diisopropylethylamine and a catalytic amount of DMAP in 97% yield. Treatment of **7** with tetrabutyl ammonium fluoride (TBAF) yielded the alcohol, which underwent smooth tosylation to yield the corresponding tosylate **8** in 94% yield. Deprotection of the MOM ether in **8** was envisioned to yield the hydroxy tosylate **5a**, a precursor for the Williamson ether formation. However, we were pleased to find that the reaction of **8** with $FeCl_3 \cdot 6H_2O$[12] resulted in the simultaneous deprotection of MOM and acetonide as well as cyclization to form the tetrahydrofuran **9** in 66% yield as a single diastereomer. As for the mechanism, on the basis of the observed high stereoselectivity, we believe that the reaction is proceeding through a S_N2-type substitution.[13] Tetrahydrofuran **9** was transformed into its silyl ether **10**, which was then subjected to the ozonolysis under modified Criegee conditions.[14] Ozonolysis in MeOH/dichloromethane (DCM),

SCHEME 3. Synthesis of (+)-2,5-bis-*epi*-Goniothalesdiol



followed by treatment of the resultant methoxyhydroperoxide with acetic anhydride/Et_3N/DMAP in refluxing benzene, produced the goniothalesdiol bis silyl ether **11** in 66% yield along with 22% of the corresponding aldehyde. Deprotection of the silyl ether in **11** produced the natural enantiomer of goniothalesdiol (+)-**1** in 75% yield. Synthetic **1**, $[\alpha]_D$ +7.1 (*c* 0.3, EtOH), lit[3] $[\alpha]_D$ +7.5 (*c* 0.23, EtOH), showed physical and spectroscopic data identical to those described for the natural (+)-goniothalesdiol (Scheme 2).

Regioselective hydroxy tosylate **5b** was synthesized employing simple synthetic transformations. Attempts to convert the hydroxy tosylate **5b** into the tetrahydrofuran by NaH mediated ether formation were unsuccessful, which can be attributed to the strain involved in the formation of the 5,5-trans ring junction. It was gratifying to find that the reaction of hydroxy tosylate **5b** with $FeCl_3 \cdot 6H_2O$ cleanly produced the tetrahydrofuran **12** in very high yield with complete selectivity. Ozonation of the terminal olefin in **12** in MeOH/DCM, followed by treatment of the resultant methoxyhydroperoxide with acetic anhydride/Et_3N/DMAP in refluxing benzene, produced methyl ester **13** in 70% yield. Deprotection of the acyl groups under standard conditions produced (+)-2,5-bis-*epi*-goniothalesdiol **2** (Scheme 3).

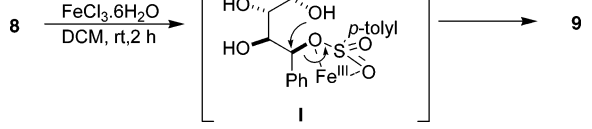
In summary, an efficient stereoselective synthesis of natural (+)-goniothalesdiol was accomplished starting from D-tartaric acid. A convenient and general method for the stereoselective synthesis of substituted tetrahydrofuran was developed. In the present sequence, starting from the tartaramide **3**, goniothalesdiol and 2,5-bis-*epi*-goniothalesdiol were obtained in ~20 and 28% overall yields, respectively.

Experimental Section

Preparation of (2*S*,3*S*,4*S*,5*R*)-2-(But-3-enyl)-tetrahydro-5-phenylfuran-3,4-diol (9): To a solution of **8** (0.65 g, 1.3 mmol) in dry DCM (16 mL) was added $FeCl_3 \cdot 6H_2O$ (1.43 g, 5.3 mmol) under an argon atmosphere. After stirring for 2 h at room temperature, it was filtered through a pad of Celite, and the Celite pad washed with ether (20 mL). The ethereal layer was washed with a saturated solution of $NaHCO_3$ (10 mL) and brine (20 mL) and dried (Na_2SO_4). Evaporation of the solvent and silica gel column chromatography of the residue using petroleum ether/ethyl acetate (6:4) as an eluent yielded the tetrahydrofuran **9** (0.21 g, 66%) as a white solid: mp 124−126 °C; $[\alpha]_D$ +21.5 (*c* 0.9, $CHCl_3$); IR (neat) 3565, 3405, 2915, 1641, 1562, 1392, 1286, 1110, 1022, 912, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54−2.05 (m, 4H), 2.10−2.42 (m, 2H), 3.96−4.24 (m, 3H), 4.62 (d, 1H, J = 3.9 Hz),

(12) For use of $FeCl_3$ in the deprotection of acetals and the formation of ethers, see: (a) Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684. (b) Sharma, G. V. M.; Kumar, K. R.; Sreenivas, P.; Krishna, P. R.; Chorghade, M. S. *Tetrahedron: Asymmetry* **2002**, *13*, 687. It is worth noting that 1,4-diol **5** failed to produce the tetrahydrofuran under similar conditions.

(13) Hydrolysis of acetals/ketals with $FeCl_3 \cdot 6H_2O$ is already well-documented in literature.[12] We believe that in the present sequence, $FeCl_3 \cdot 6H_2O$ is transforming the bisketal into the triol (**I**). The formation of THF from triol **I** is proceeding probably through the chelation of Fe^{3+} with the tosylate, weakening the C−OTs bond, thereby facilitating the intramolecular S_N2 displacement leading to the product.



(14) (a) Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363. (b) Criegee, R. *Ber. Bunsen-Ges. Phys. Chem.* **1944**, *77*, 722. For an oxidative cleavage of olefins to the corresponding methyl esters, see: (c) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675.

4.88−5.20 (m, 2H), 5.88 (ddt, 1H, J = 16.8, 10.2, 6.6 Hz), 7.216−7.58 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.9, 30.2, 79.2, 80.7, 85.5, 86.2, 115.1, 125.9, 127.8, 128.6,138.1, 140.1; HRMS for $C_{14}H_{18}O_3$ + Na calcd, 257.1156; found, 257.1154.

Preparation of Goniothalesdiol bis-*tert*-Butyldimethylsilyl Ether (11): Ozone was bubbled through a pre-cooled (−70 °C) solution of **10** (0.12 g, 0.26 mmol) in MeOH/DCM (1:9; 15 mL), containing a trace of $NaHCO_3$ (80 mg), until the pale blue color persisted. Excess ozone was flushed off with oxygen. The solvent was evaporated under reduced pressure, and the residue was dissolved in dry benzene (12 mL). Triethylamine (0.4 mL, 2.6 mmol), acetic anhydride (0.2 mL, 1.82 mmol), and a catalytic amount of DMAP (16 mg) were added to the reaction mixture and refluxed for 4 h. It was then cooled, diluted with water (10 mL), and extracted with ether (3 × 10 mL). The combined ethereal extract was washed with brine (15 mL) and dried (Na_2SO_4). Evaporation of the solvent and silica gel column chromatography of the residue using petroleum ether/ethyl acetate (96:4) as an eluent yielded **11** (0.085 g, 66%) as colorless oil: $[\alpha]_D$ +19.8 (*c* 1, $CHCl_3$); IR (neat) 2954, 2929, 2857, 1743, 1650, 1562, 1470, 1390, 1257 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.13 (s, 3H), −0.04 (s, 3H), −0.02 (s, 3H), 0.00 (s, 3H), 0.76 (s, 9H), 0.85 (s, 9H), 1.80−2.28 (m, 2H), 2.38−2.66 (m, 2H), 3.61 (s, 3H), 3.84 (dd, 1H, J = 3.0, 1.5 Hz), 3.95 (s, 1H), 4.08 (dt, 1H, J = 7.8, 4.5 Hz), 4.65 (d, 1H, J = 1.5 Hz), 7.08−7.30 (m, 3H), 7.34 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, −4.54, −4.49, −4.4, 17.8, 18.0, 24.7, 25.6, 25.7, 31.1, 51.5, 80.0, 81.1, 85.5, 88.9, 126.7, 127.1, 128.0, 141.0, 174.1; HRMS for $C_{26}H_{46}O_5Si_2$ + Na calcd, 517.2784; found, 517.2782.

Preparation of (+)-Goniothalesdiol (1): To a solution of **11** (76 mg, 0.15 mmol) in dry THF (4 mL) cooled to 0 °C was added TBAF (0.2 g, 0.6 mmol). The solution was slowly allowed to warm to room temperature. After stirring for 2 h at room temperature, saturated NH_4Cl (3 mL) was added, and the solution was extracted with ether (3 × 10 mL). Combined ethereal extracts were washed with brine (15 mL) and dried (Na_2SO_4). To the residue obtained after evaporation of solvent was added dry MeOH (3 mL) and Amberlyst-15 (0.12 g) and stirred for 1 h at room temperature. It was passed through a pad of Celite. Evaporation of the solvent and silica gel column chromatography of the residue using petroleum ether/ethyl acetate (1:1) as an eluent afforded goniothalesdiol (31 mg, 75%) as a yellow oil: $[\alpha]_D$ +7.1 (*c* 0.3, EtOH), lit[3] $[\alpha]_D$ +7.5 (*c* 0.23, EtOH); IR (neat) 3448, 2930, 1735, 1588, 1454, 1370, 1234, 1176, 1072, 904, 856, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98−2.26 (m, 2H), 2.35−2.80 (m, 4H), 3.69 (s, 3H), 4.02−4.21 (m, 3H), 4.61 (d, 1H, J = 4.8 Hz), 7.22−7.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 30.5, 51.9, 79.0, 80.7, 85.3, 86.2, 126.1, 127.8, 128.5, 139.9, 174.6; HRMS for $C_{14}H_{18}O_5$ + Na calcd, 289.1054; found, 289.1052.

Acknowledgment. We thank Department of Science and Technology (DST), New Delhi, for funding of this project. S.L.G. thanks Council of Scientific and Industrial Research (CSIR), New Delhi, for a junior research fellowship.

Supporting Information Available: Experimental procedures and spectroscopic data for the compounds and copies of ^{1}H NMR, ^{13}C NMR, and HRMS spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org

JO060159F