# CHIRAL TETRAHYDROFURAN SYNTHESIS FROM D-RIBOSE DIPHENYL DITHIOACETAL

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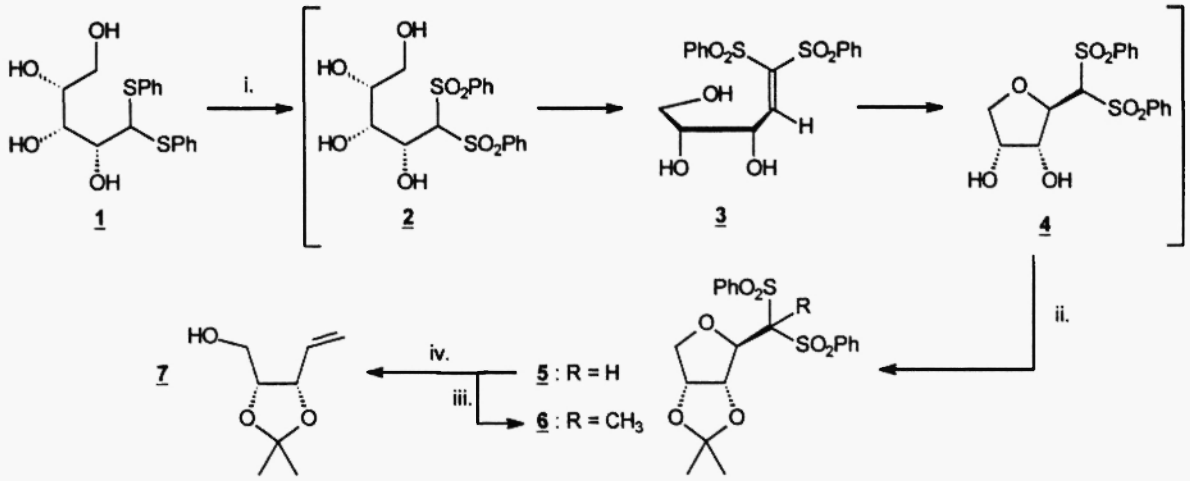
**Abstract**: Treatment of D-ribose diphenyl dithioacetal **1** with 4.2 equivalents of *m*-CPBA results in formation of the bis(phenylsulfone) **4**, which is likely the result of an oxidation-elimination-cyclization sequence. Tetrahydrofuran **4** is protected as the isopropylidene derivative **5**. The latter is alkylated to generate **6**, and **5** undergoes reductive elimination to the olefin **7**.

The synthesis of enantiomerically pure functionalized tetrahydrofuran (THF) and tetrahydropyran (THP) derivatives is of major importance in natural products synthesis since these heterocyclic motifs are found in numerous biologically active compounds (1). Methodologies have been developed from achiral starting materials (2), as well as from enantiomerically pure materials such as carbohydrates (3). This communication details the synthesis of a chiral polyhydroxylated THF from D-ribose diphenyl dithioacetal **1**, and initial experiments on the subsequent manipulation of the bis(phenylsulfone) group. Similar preparations of polyhydroxylated THFs and THPs are known in the carbohydrate field, primarily using diethyl dithioacetals (4), however further manipulation of the bis(ethylsulfone) function has been of limited use.

D-Ribose diphenyl dithioacetal **1** is available from D-ribose *via* mercaptalation with benzenethiol (5). Oxidation of **1** with excess *m*-CPBA (4.2 equivalents) results in a one-pot sequence of reactions that yields THF bis(phenylsulfone) **4**, isolated and characterized as the isopropylidene derivative **5** (50% from **1**, Scheme). The formation of THF **4** is likely the consequence of a series of events beginning with exhaustive oxidation of **1** to the corresponding bis(phenylsulfone) **2**. Spontaneous elimination of water from **2** generates a ketene bis(phenylsulfone) **3** which is subsequently attacked by the hydroxyl at C-5 to form the THF ring. The stereochemical outcome of the cyclization step is most probably a consequence of the orientation of the allylic hydroxyl group in **3**. The lower energy transition state for this 5-exo-trig cyclization (6) would have the allylic OH in **3** *anti* to the large bis(phenylsulfonyl) function, resulting in the indicated THF **4**. Such selectivity has been observed in other cyclizations involving sugar-derived ketene bis(sulfones) (7).

Protecting **4** as isopropylidene **5** allows for complete stereochemical assignment of the THF group. The $^1$H NMR spectrum of **5** in DMSO-$d_6$ (8) shows a doublet for the acidic bis(phenylsulfone) proton at 6.30 ppm ($J_{1,2}$ = 7.1 Hz) which disappears upon addition of $D_2O$. With H-D exchange at C-1, the signal for H-2 at 4.56 ppm collapses to a narrow doublet with $J_{2,3}$ = 1.5 Hz, a coupling that can only be reconciled with the "β" configuration shown in **4** and **5**.




Scheme: i. *m*-CPBA (4.2 eq), $CH_2Cl_2$, RT. ii. $(CH_3)_2C(OCH_3)_2$, DMF, TsOH. iii. NaH, $CH_3I$, DMF, 80 °C. iv. Mg, MeOH, 50 °C.

Alkylation of **5** with NaH and methyl iodide affords methyl derivative **6** as the only product (76%) (8). This reaction presumably proceeds *via* a bis(phenylsulfonyl) anion which would be potentially capable of undergoing β-elimination with opening of the THF ring. Isolation of **6** as the only product suggests that β-elimination does not occur in this system. Treatment of **5** with Mg in refluxing methanol, in an attempt to reduce the bis(phenylsulfonyl) group, results in the olefin **7** (80%) (8). Current work centers on the reclosure of olefins such as **7** to form optically pure THFs (9).

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**References and Notes**:

(1) For lead examples see K.C. Nicolaou and E.J. Sorensen, *Classics in Total Synthesis : Targets, Strategies, Methods*, Weinheim VCH, NY, (**1996**).
(2) For a general review on THF and THP synthesis see: T.L.B. Boivin, *Tetrahedron*, 43, 3309 (**1987**).
(3) See R.L. Dorta, A. Martin, J.A. Salazar, E. Suarez, and T. Prange, *J. Org. Chem.*, 63, 2251 (**1998**) and references therein.
(4) J.D. Wander and D. Horton, *Adv. Carbohydr. Chem. Biochem.*, 32, 15 (**1976**).
(5) J.D. Wander and D. Horton, *J. Org. Chem.*, 39, 1859 (**1974**).
(6) J.E. Baldwin, *J. Chem. Soc., Chem. Comm.*, 734 (**1976**).
(7) P. Norris, D. Horton and D.E. Giridhar, *Tetrahedron Lett.*, 37, 3925 (**1996**).
(8) Compound **5**: $[\alpha]_D$ –45.5° (*c* 0.05, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $D_6$-DMSO): δ 1.22 (s, 3H); 1.38 (s, 3H); 3.35 (dd, 1H, *J* = 4.0, 10.7 Hz, H-5); 3.56 (d, 1H, *J* = 10.6 Hz, H-5'); 4.55 (dd, 1H, *J* = 7.1, 1.5 Hz, H-2); 4.72 (dd, 1H, *J* = 3.8, 6.0 Hz, H-4); 5.22 (d, 1H, *J* = 6.0 Hz, H-3); 6.30 (d, 1H, *J* = 7.1 Hz, H-1); 7.48-7.94 (m, 10H, $SO_2Ph$). Compound **6**: $[\alpha]_D$ –32.2° (*c* 0.023, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$): 1.35 (s, 3H); 1.50 (s, 3H); 1.66 (s, 3H); 3.78 (dd, 1H, *J* = 2.5, 10.0 Hz, H-5); 4.16 (dd, 1H, *J* = 6.2, 10.0 Hz); 4.52 (d, 1H, *J* = 3.3 Hz, H-2); 4.86 (m, 1H, H-4); 5.40 (dd, 1H, *J* = 3.3, 6.6 Hz, H-3); 7.46-8.08 (m, 10H, $SO_2Ph$). Compound **7**: $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H); 1.51 (s, 3H); 3.59 (m, 2H, H-5, H-5'); 4.24 (dd, 1H, *J* = 6.2, 12.0 Hz, H-4); 4.63 (dd, 1H, *J* = 7.1, 6.8 Hz, H-3); 5.27 (ddd, 1H, *J* = 0.4, 1.1, 12.0 Hz, H-1 vinyl); 5.37 (ddd, 1H, *J* = 0.4, 1.7, 17.0 Hz, H-1' vinyl); 5.83 (ddd, 1H, *J* = 7.0, 11.0, 17.0 Hz, H-2, vinyl).
(9) M.H.D. Postema, *C-Glycoside Synthesis*, CRC Press, 103 (**1995**).

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