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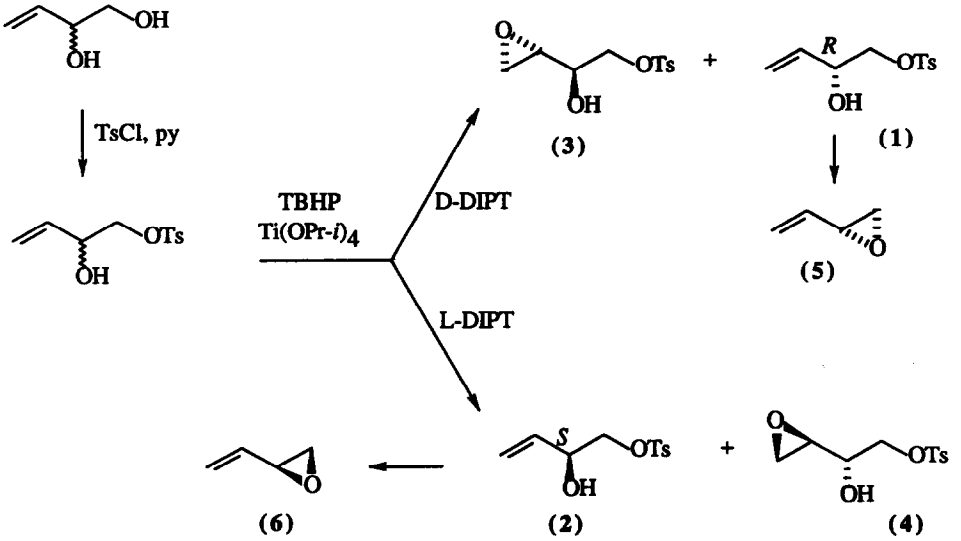
Synthesis of Enantiomerically Pure 3-Butene-1,2-diol Derivatives via a Sharpless Asymmetric Epoxidation Route.

Constantin Neagu and Tapio Hase*

Department of Chemistry, University of Helsinki, Vuorikatu 20, Helsinki 10, Finland

Abstract: A short enantiospecific synthesis of the butenediol monotosylates (1,2), the epoxybutanediol monotosylates (3,4) and the epoxybutenes (5,6) is described.

The title chiral C_4 molecules are small, polyfunctional building blocks which makes them attractive precursors for the synthesis of numerous natural products[1]. Apart from their synthetic potential, we recently required such compounds for use as chromatographic standards in toxicological studies of butadiene metabolites. We now describe the synthesis of (*R*)-(+)- and (*S*)-(-)-1-tosyloxy-3-buten-2-ol (**1,2**), (2*R*,3*S*)-(-)- and (2*S*, 3*R*-(+)-1-tosyloxy-3,4-epoxybutan-2-ol (**3,4**), and (*R*)-(-)- and (*S*)-(+)-3,4-epoxy-1-butene (**5,6**), relying on kinetic resolution by means of the Sharpless asymmetric epoxidation as the key step. The synthesis of (**1-4**) consists of two steps (Scheme) from the readily available racemic 3-butene-1,2-diol[2]; the synthesis of these compounds as the pure enantiomers has not been reported previously except for a 4-step route to (**1**) in the patent literature[3], involving the enzymatic kinetic resolution of 3-acetoxy-4-tosyloxy-1-butene[4,5]. The Sharpless procedure can of course be operated, by proper choice of reagents, to give direct access to either enantiomer which is not the case in the enzymatic resolution. The actual oxidation products (**3,4**) in the Sharpless route are interesting starting materials in their own right for the synthesis of optically active natural products, and are reported here for the first time.



Racemic 3-butene-1,2-diol, an isomerization product[2] of commercially available *cis*-2-butene-1,4-diol, undergoes selective tosylation at the primary OH group in 94.3 % yield, using a 1:1.5:2 ratio of the

diol, tosyl chloride and pyridine, respectively, in chloroform[5,6]. The subsequent kinetic resolution of racemic 1-tosyloxy-3-buten-2-ol under the Sharpless epoxidation conditions[7] using *t*-butylhydroperoxide (TBHP), titanium(IV) isopropoxide and D-(-)-diisopropyltartrate (D-DIPT) (CH_2Cl_2, -5 °C) gave (*R*)-(+)-1-tosyloxy-3-buten-2-ol (**1**) in 95 % yield (ee 85 %), and (2*R*,3*S*)-1-tosyloxy-3,4-epoxybutan-2-ol (**3**) in 90 % yield (ee 95 %). Recrystallization furnishes enantiomerically pure compounds (ee > 99%). Kinetic resolution using L-DIPT under the same conditions afforded (*S*)-(-)-1-tosyloxy-3-buten-2-ol (**2**) and (2*S*,3*R*)-1-tosyloxy-3,4-epoxybutan-2-ol (**3**) in similar yields and enantiomeric purities. (**1**) and (**2**) may be converted to the vinyl epoxides[5] (**5**,**6**) with NaH in DMSO in high yield.

The mechanistic background[8] of the Sharpless asymmetric epoxidation allows the prediction of the absolute configuration of the resulting chiral epoxide based upon the configuration of the catalytic complex. The absolute configuration assigned was further confirmed by analysis of the ^{1}H-nmr spectra of the diastereomeric mixtures obtained by derivatization of each chiral substrate with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride[9] (MTPA-Cl). The diastereomers formed exhibit chemical shift nonequivalence; the assignment of absolute configuration of the starting enantiomers can be confirmed using ^{1}H-nmr configurational correlation schemes[10]. The enantiomeric purity was determined by ^{1}H-nmr and ^{19}F-nmr analysis of the corresponding MTPA diastereomers[10]. A more accurate determination of enantiomeric purity came from the HPLC analysis of the synthesized diastereomers.

We expect that (**1**-**6**) will prove highly versatile starting materials for natural product synthesis, either as chiral C4 units, or, after ozonolysis, sources of glyceraldehyde chirons. We will report in our full paper on a specific application.

(*S*)-1-tosyloxy-3-buten-2-ol (**2**): m.p. 58-59 °C, $[\alpha]_D$ -3.85° (c 1.0, CH_3OH).
(2*S*,3*R*)-1-tosyloxy-3,4-epoxybutane-2-ol (**4**): m.p. 25-6 °C, $[\alpha]_D$ +0.51 (c 0.81, $CHCl_3$); ^{1}H nmr (200MHz, $CDCl_3$) δ 4.18 (1 H, dd, 10.58, 3.9 Hz), 4.11 (1 H, dd, 10.63, 5.2 Hz), 3.91 (1H, dt, 11.38, 4.74 Hz), 3.04 (1H, ddd, 11.38, 3.64, 0.73 Hz); ^{13}C nmr ($CDCl_3$) δ 44.2 (t), 51.0 (d), 67.9 (d), 70.6 (t).
(*S*)-3,4-epoxy-1-butene (**6**): b.p. 66°C, $[\alpha]_D$ +0.16° (c 0.057, CH_3CN); δ 2.64 (1 H, dd, 2.69, 2.61 Hz), 2.95 (1 H, dd, 5.25, 4.11 Hz), 3.32 (1 H, br m), 5.36 (1 H, br m), 5.54 (2 H, br m); δ 49.22 (t), 53.05 (d), 120.09 (d), 136.5 (t).

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