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Resolution of *cis*-4-*O*-TBS-2-Cyclopenten-1,4-Diol

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Abstract: The resolution of *cis*-4-*O*-TBS-2-cyclopenten-1,4-diol with a few different enzymes in organic medium is described. The optical purity and yield of both the alcohol and acetate were moderate to excellent.

The preparation of optically active *cis*-2-cyclopenten-1,4-diol derivatives has been the topic of numerous papers.[1] The utility of such compounds has been manifested in the preparation of prostaglandins[2] and carbocyclic nucleosides.[3] Notably, desymmetrization of meso-2-cyclopenten-1,4-diol or meso-cyclopenten-1,4-diacetates as well as resolution of 4-acetoxy-cyclopentenone or its ketal appear to be the methods of choice in the literature. While these are excellent methods, the resolution of the acetoxy-cyclopentenone derivatives suffers from throwing 1/2 of the material away. This can be improved or avoided in part by racemization and recycling. In the resolution of meso-compounds, specifically *cis*-2-cyclopenten-1,4-diol, many procedures give rise to significant amounts (30-40%) of diacetate.[1c,d] Interestingly, substituents on the cyclopentenyl ring system have improved the yield. Poor yield is not a problem with the deacylation of diacetates.[1j] For the enantiopode that we desired (1*R*,4*S*), the option using PLE[1k] did not meet our optical activity criterion.

We were interested in a process to generate optically active *cis*-2-cyclopenten-1,4-diol derivatives in which we could use both resolved materials to prepare identical carbocyclic isomers. Such a process would require that the enantiomeric purity of each product from the resolution would need to be >95%. Herein, we communicate the resolution of *cis*-4-*O*-TBS-2-cyclopenten-1,4-diol[4] using 3 different enzymes in TBME with isopropenyl or vinyl acetate as acylating agent. The results are shown in Scheme 1 and Table 1. As can be seen in the table, pancreatin in TBME/Et_3N with vinyl acetate (entry 1) gave the best result and met our criterion for synthesis. Lyphozyme IM gave good ee's of both acetate and alcohol but in poorer yield (entry 2). Sp 435 with isopropenyl acetate gave an excellent ee of the alcohol, but the optical purity of the acetate was poor (entry 3). Alcohol **2** was converted into acetate **4** in 98% yield (crude), and the acetates were adequately separated by GC chiral column to assess optical purities.[5] The optical purity of both acetates were >98% (entry 1). Desilylation provided mono-acetate **5**, containing the same handedness as silyl ether **2**, in high optical purity and 67-77% yield. This allows for the conversion of alcohols **2** and **5** into analogous, isomeric carbocyclic compounds.

Pancreatin Procedure: Alcohol **1** (119 mmol) in TBME (150 mL) was treated sequentially with Et_3N (0.7 equiv), pancreatin (3 equiv wt), and vinyl acetate (5 equiv). The resulting slurry was stirred for 6-24 h (monitored by GC[6]), filtered, concentrated *in vacuo*, and purified via chromatography on SiO_2 (gradient elution 5% EtOAc/hex to 20% EtOAc/hex) to provide desired acetate **3**, 14.7 g, 48% yield (>98%ee), and alcohol **2**, 11.8 g, 47% yield (acetate derivative **4** analyzed >98%ee). For **2**: R_f = 0.2, 20% EtOAc/hex; ^1H NMR ($CDCl_3$, 300 MHz) 5.93 (dt, 1H, *J*= 5.5, 1.7 Hz), 5.84 (dt, 1H, *J*= 5.5, 1.6 Hz), 4.6 (m, 1H), 4.5 (m, 1H), 2.8 (s, 1H), 2.69 (dt, 1H, *J*= 13.8, 7.1 Hz), 1.52 (dt, 1H, *J*= 13.8, 4.7 Hz), 0.90 (s, 9H), 0.09 (s, 6H). For **3**: R_f = 0.5, 5% EtOAc/hex; ^1H NMR ($CDCl_3$,) 6.0 (m, 1H), 5.9 (m, 1H), 5.5 (m, 1H), 4.7 (m, 1H), 2.8 (m, 1H), 2.05 (s, 3H), 1.6 (m, 1H), 0.91 (s, 9H), 0.09 (s, 6H).

Scheme 1

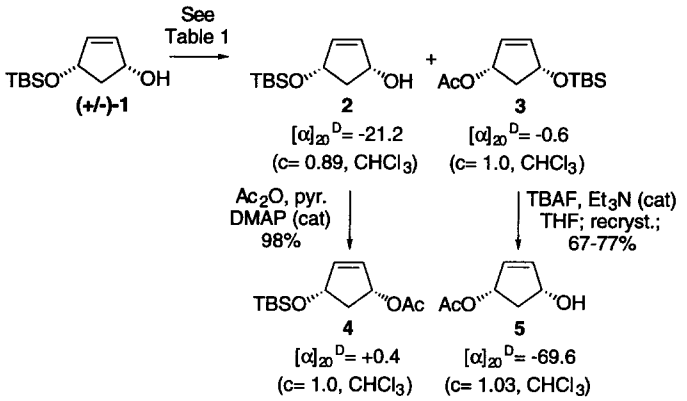

Table 1: Enzymatic Resolution of mono-TBSO-cyclopentenol 1.

Entry	Enzyme (equiv wt)	Conditions: Solvent, Reagents* (equiv), Time (h)	%Yield 2 (%ee)	%Yield 3 (%ee)
1	Pancreatin (3)	TBME, VA (5), Et_3N (0.7), 7	47 (98)	48 (98)
2	Lyphozyme IM (3)	TBME, VA (4), 5	39 (98)	37 (94)
3	Sp435 (0.3)	TBME, IA (3), 5.5	33 (98)	53 (57)

*All reactions were run at rt. VA= vinyl acetate; IA= isopropenyl acetate. Optical purity was assessed by GC chiral col. analysis of acetates **3** and **4**.

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5. CDX-β, 10m x 0.25mm id, 0.25 μm film (J&W Scientific); linear velocity (He) = 80 cm/sec; inj., 200 °C; det., 220 °C; oven, 100 °C. t_R (**4**) = 18.3 min; t_R (**3**) = 19.2 min. All compounds gave adequate spectral analyses (^{1}H NMR, ^{13}C NMR, IR, MS) and were at least 98% pure by GC.

6. The reaction was judged to be complete when a 55:45 mixture of **3**:**2** was observed by GC on HP-5, 30 m x 0.32 mm; inj., 200 °C; detector, 275 °C; oven (gradient), 100 °C (10 min) increase 10 °C /min to 200 °C (hold 5 min). t_R (**2**) = 13.95 min, t_R (**3**) = 17.47 min.

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