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The Synthesis of Optically Active Derivatives of Erythritol

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***Abstract** : The acetonides **2** and **4**, obtained from erythritol, are excellent substrates for SAM II lipase. The resulting homochiral mono-esters **3** and **5** are suitable chiral building blocks.*

Methods for the preparation of optically active butanetetrol derivatives are of particular interest. They are important building blocks for the synthesis of biologically active molecules such as arachidonic acid metabolites (HETE's[1], di-HETE's[2], leukotrienes[3]), nucleosides[4] and other molecules of biological interest[5].

While treitol derived compounds are easily obtainable from D- and L-tartaric acids, homochiral erythritol derivatives have been less accessible. Recently the latter have been obtained from L-ascorbic acid and D-isoascorbic acid[6,7].

As part of a program devoted to the enzyme catalyzed synthesis of chiral building blocks[8], we wish to describe here a practical approach to selectively protected homochiral erythritol derivatives **3** and **5** starting from commercially available erythritol. The meso-diol **2** was prepared from **1** in a 3-step sequence via selective protection of the primary hydroxyl groups as pivalate esters, acetalization and ester hydrolysis.

Enzyme catalyzed transesterification[9] with vinyl acetate and SAM-II lipase[10] yielded mono-acetate (+)-**3** in high optical purity (95 % ee)[11]. On the other hand, hydrolysis of dibutyric ester **4**, easily prepared from **2**, with the same lipase in a phosphate buffer at pH 7 afforded mono-butyrate (-)-**5** (97 % ee)[11].

In order to illustrate the potential use of these chiral building blocks and to prove their absolute configuration, (+)-**3** and (-)-**5** were transformed into the four epoxides (+)-**9** and (-)-**9**, and (+)-**10** and (-)-**10**. Essential for the transformations is the acid catalyzed isomerization of the 2,3-acetonides to 1,2-acetonides. This proceeded uneventfully when the primary hydroxyl group was protected as a silyl ether (route j, f, k). Subsequently, intermediates (+)-**6**[12] and (-)-**6**[12] afforded respectively the pairs of epoxides (+)-**9**[12], (-)-**10**[12] and (-)-**9**[12], (+)-**10**[12]. Interestingly, all 4 epoxides can be obtained from either one of the two initial chiral building blocks **3** or **5**. This became possible when it was observed that tin(II)-chloride or boron trifluoride mediated transacetalization, at 0°C, of (+)-**3** and (-)-**5** occurred much faster than acyl migration (route e). With p.toluenesulfonic acid as a catalyst partial racemisation was found.

With the formation of these epoxides, the absolute configurations of the compounds shown in the scheme are proven, as (+)-**9** and (-)-**10** have been obtained from D-isoascorbic acid and (-)-**9** and (+)-**10** from L-ascorbic acid[6].

In summary, we have demonstrated that erythritol can be transformed efficiently in both (-)-**5** or (+)-**3** in very high optical purity, via either lipase-catalyzed hydrolysis of **4** or transesterification of **2** respectively.

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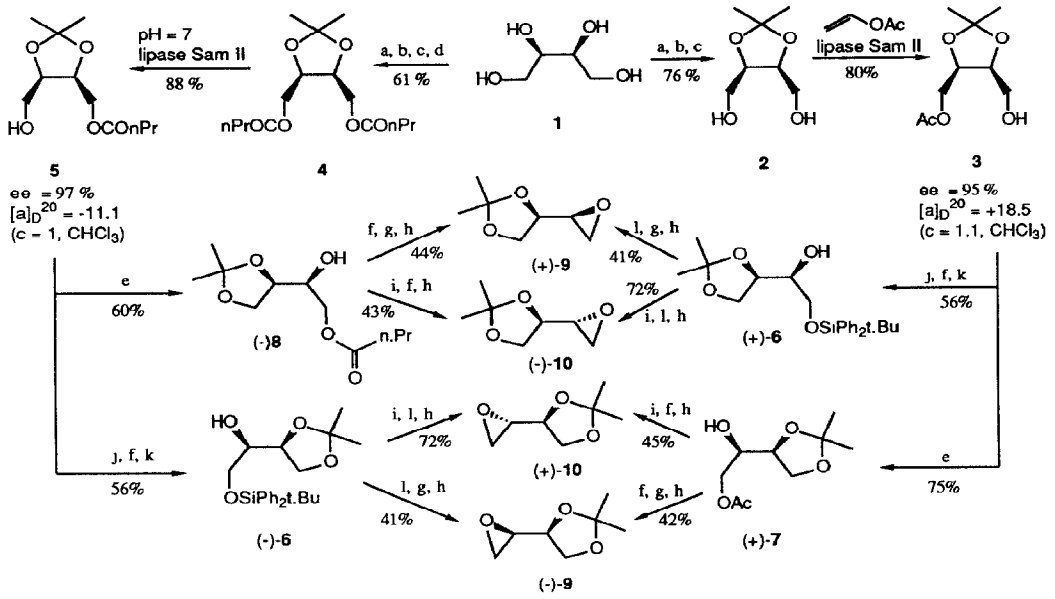

a) $(CH_3)_3CCOCl$, pyridine; b) 2,2-dimethoxypropane, pTSA; c) KOH, MeOH; d) nPrCOCl, CH_2Cl_2, Et_3N; e) acetone, BF_3OEt_2, 0°C; f) K_2CO_3, MeOH, rt.; g) TsCl, pyridine, 0°C; h) KOtBu, THF; i) MsCl, NEt_3, CH_2Cl_2,-10°C; j) $tBuPh_2SiCl$, imidazole, DMF; k) acetone, pTSA; l)TBAF, THF.

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10. From *Pseudomonas sp.* (Amano Pharm. Co., supplied by Fluka).

11. Determined by GC-analysis of the corresponding Mosher-ester.

12 $[\alpha]_D^{20}$-values : (+)-**6** : +1.96 (c = 1.38 $CHCl_3$); (-)-**6** : -1.06 (c = 1.014 $CHCl_3$); (+)-**7** : +8.03 (c = 1.3 $CHCl_3$); (-)-**8** : -6.2 (c = 0.95 $CHCl_3$); (+)-**9** : +9.9 (c = 1 EtOH); (-)-**9** : -10.7 (c = 0.88 EtOH); (+)-**10** : -0 97 (c = 0.92 EtOH); (-)-**10** : -1 01 (c = 1.38 EtOH).