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Enzymatic Preparation of Optically Active 2-Acetoxymethylglycidol, A New Chiral Building Block in Natural Product Synthesis.

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Abstract : Asymmetric hydrolysis of geminally disubstituted achiral diacetate **2** with lipase PPL yielded optically active (R)-(-)-2-acetoxymethylglycidol **3** and its reduction gave compound **6**, useful as the *tert*-alcohol chiral building block.

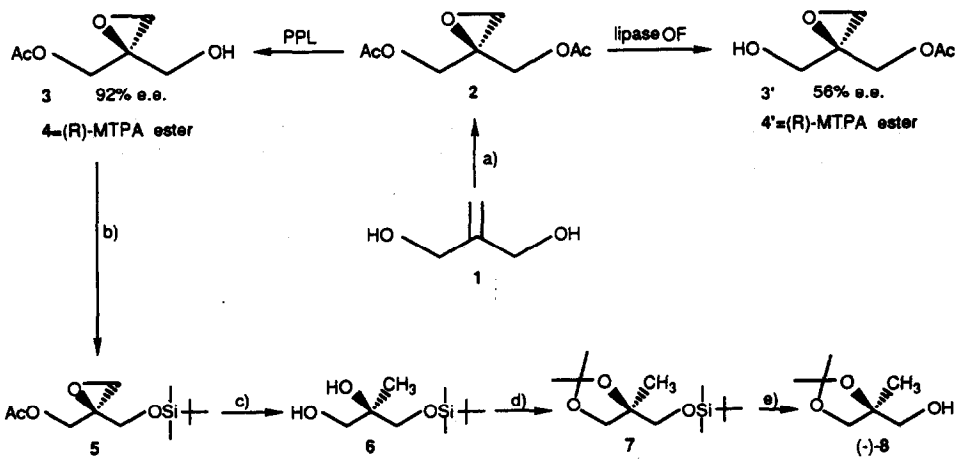
In the chiral synthesis of biologically active substances, optically active epoxides and alcohols are those of the most useful chiral building blocks such as Sharpless epoxide, α-hydroxy acid, β-hydroxy ester, β-hydroxy ketone, diol and so on. In these kinds of chiral building blocks, only a few papers were reported about general *tert*-alcohol chiral synthon[1-3].

Thus, in this paper, we report simple preparation of chiral building block which yield optically active *tert*-alcohol by asymmetric hydrolysis of achiral diacetate with lipase PPL (Pig pancreatic lipase). The optically active epoxy alcohol, such as **3**, is a versatile chiral building block for the natural products syntheses because it can be used as both R- and S- units. Further the reduced compound **6** which has methyl substituted tertiary carbinol skeleton is also a useful building block for the chiral syntheses of frontalin[4], bicyclomycin[5] and α-tocopherol[6].

The substrate, achiral diacetate **2** was conveniently prepared from 2-methylene-1,3-propanediol **1**[7] by acetylation (Ac_2O/pyridine) and subsequent epoxidation with m-chloroperbenzoic acid (MCPBA 2,2 equiv., CH_2Cl_2 ; 70% yield for 2 steps). PPL and lipase OF (*Candida cylindracea*) were chosen as hydrolyzing enzymes[8] due to the modest price, and PPL provided the expected optically active epoxy alcohol **3** in good yield.

When the diacetate **2** in acetone and 0.1M phosphate buffer (pH 6.5) was treated with PPL at 0°C for 7 hr, a dextrorotatory epoxy alcohol (-)-**3** ($[\alpha]_D$-4.0° ,Et_2O) was obtained in 77% yield. On the other hand, lipase OF treatment gave the antipode (+)-**3'** ($[\alpha]_D$+2.2° , Et_2O).

The enantiomeric purity was estimated as 92% e.e. by HPLC analysis of the corresponding (R)-α-methoxy-α-(trifluoromethyl)phenylacetate[9] **4** (MTPA ester of **3**). In order to determine the absolute configuration, (-)-**3** was converted to (-)-**8** ($[\alpha]_D$-4.8° , CH_2Cl_2) (scheme) and this was compared with the authentic sample (S)-(-)-**8** (lit[5]. $[\alpha]_D$-5.33° , CH_2Cl_2), therefore, the absolute configuration of (-)-**3** was assigned to be R



a) 1. Ac_2O/pyridine 2. MCPBA/CH_2Cl_2 b) ClSiMe$_2$-*t*-Bu,DMAP/Et_3N,DMF c) LAH/Et_2O
d) acetone, *p*-TsOH e) *n*-Bu_4NF/THF
*$[\alpha]_D^{22}$ values ; **3**:-4.0° (c=1.0, Et_2O) ; **5**:-4.1° (c=4.5, Et_2O) ; **6**:+0.2° (c=5.0, Et_2O) ; **7**:+2.3° (c=2.0, Et_2O) ; (-)-**8**:-4.8° (c=2.0, CH_2Cl_2)

on the basis of the optical rotation measured.

In conclusion, we prepared a new chiral building block , (-)-2-acetoxymethylglycidol **3**, in high optical purity by asymmetric hydrolysis and established its absolute configuration as R , and its reduction product (+)-**6** is expected as a useful chiral synthon in natural products syntheses.

Syntheses of some bioactive compounds using these chiral building blocks are now under way in our laboratory.

Experiment : Enzyme PPL(1.18g) and substrate **2**(1.18g, 6.3mmol) are added to acetone(100ml) and 0.1M phosphate buffer solution(pH 6.5, 200ml) and the mixture is vigorously stirred at 0°C while pH 6.5 is maintained by continuous addition of 0.1N NaOH solution using pH controller. After about 7 hr, the mixture is saturated with NaCl and extracted with EtOAc. The organic extract is washed with brine, dried($MgSO_4$), and concentrated *in vacuo* to give an oil which is purified by silica-gel column chromatography to give 0.71g of (-)-**3** ($[\alpha]_D$-4.0°,(c 1.0, Et_2O)).

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