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# Synthesis of Glyceryl Ethers in High Optical Purity via Ruthenium Catalyzed Asymmetric Hydrogenation

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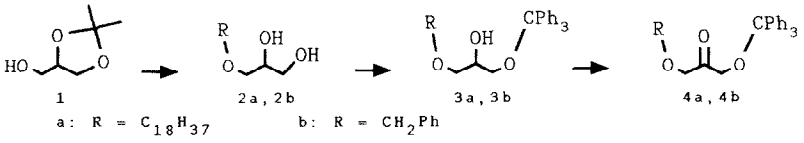
*Abstract*: 1-O-octadecyl-3-O-trityl-glycerol and 1-O-benzyl-3-O-trityl-glycerol can be prepared by asymmetric catalytic hydrogenation in O.P.> 96% and 87-88% respectively.

Optically active 1,3-glyceryl-ethers are important and versatile key building blocks for the synthesis of a large variety of compounds that are biologically important or are of interest in biochemical research like 1,2-sn-dioctaylglycerol , effective activator of protein kinase C, 1-hexadecyl-2-benzyl-sn-glycerol , important intermediate in the synthesis of platelet activating factor or 1-O-palmitoyl-2-O-benzyl-sn-glycerol, starting material for 1-O-palmitoyl-2-O-oleyl-sn-glycerol, main phospholipid of animal membranes[1,2,3].

The versatility of these intermediates is related to the presence of ether groups, e.g. trityl or benzyl, that can be selectively removed. Our goal is to find a simple method to synthetize the title compounds from achiral starting materials avoiding the general strategies which proceed from optically active 1,2-isopropylidene glycerols[4] or 3,4-isopropylidene-D-mannitol[1].

We adopt a strategy that involves the stereoselective reduction of prochiral 1,3-disubstituted derivatives of dihydroxyacetone, obtained from the corresponding racemic 1,3-glyceryl diethers by oxidative treatment, prompted on this approach by the reports on the Ruthenium-BINAP complexes, (BINAP are the atropisomeric chiral diphosphines R(+) and S(-)-Bis(diphenylphosphino)-1,1'-binaphthalene) extremely powerful catalysts for the enantioselective reduction of a large variety of prochiral ketones[5,6] .

Our strategy is applied to the synthesis of both enantiomers of 1-O-octadecyl-3-O-trityl-glycerol and of 1-O-benzyl-3-O-trityl-glycerol, two intermediates which have a high value as synthetic precursors because of the presence of trityl group that can be selectively removed by catalytic amounts of inorganic acids. The designed synthetic sequence, which starts from racemic isopropylidene glycerol, is shown in the following scheme:

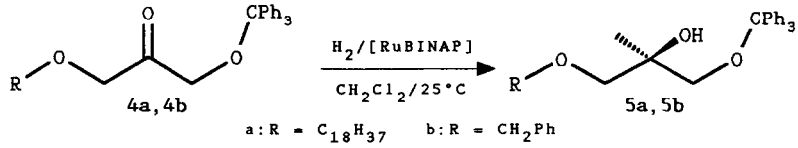



1 2a, 2b 3a, 3b 4a, 4b

a: R = $C_{18}H_{37}$ b: R = $CH_2Ph$

The compounds **2** and **3** are prepared according to literature methods[3,4]. Oxidation of **3a** and **3b** with pyridinium chlorochromate in dichloromethane gives the corresponding keto derivatives **4**[7,8].The complexes utilized for the reduction of the substrates **4a** and **4b** are the dimers $[Ru_2Cl_4((S)\text{-BINAP})_2]NEt_3$ and $[Ru_2Cl_4((R)\text{-BINAP})_2]NEt_3$ prepared according to literature methods[6]. These catalysts are capable of producing a variety of functionalized alcohols in synthetically useful enantiomeric excesses from a number of ketones[9,10] but ,to our knowledge, ketones with hydroxy protecting groups like trityl or benzyl have never been investigated. Optimum conditions for the hydrogenation reaction are as follows: the reactions are carried out in a stainless steel autoclave at 20°C under a

pressure of 100 kgw/cm$^2$ (1 kgw/cm$^2$= 9.81 x 10$^4$ Pa) of $H_2$ for 96 hours with a 0.1 M solution of the substrates in dichloromethane and with a ratio substrate to catalyst close to 100 : 1.The results of asymmetric hydrogenation are summarized in the following scheme:




4a $\xrightarrow{Ru(S)BINAP}$ (R)-(+)-5a O.P.>96% 4a $\xrightarrow{Ru(R)BINAP}$ (S)-(-)-5a O.P.>96%

4b $\xrightarrow{Ru(S)BINAP}$ (R)-(+)-5b O.P.= 88% 4b $\xrightarrow{Ru(R)BINAP}$ (S)-(-)-5b O.P.=87%

Chemically pure 1-O-octadecyl-3-O-trityl-glycerol **5a** and 1-O-benzyl-3-O-trityl-glycerol **5b** are obtained in high chemical yields (> 70 %) by flash-chromatography [11] . When the reactions are carried out in protic solvents or at higher temperature (60°C) some debenzylation and detritylation are observed. It is worth noting that the removal of the protecting groups as well as the optical yields are also strongly dependent on the purity of the ruthenium catalysts.

1-O-octadecyl-3-O-trityl-glycerol **5a** is obtained almost optically pure[12] while 1-O-benzyl-3-O-trityl-glycerol **5b** shows an O.P.ranging from 87% to 88%[12]. These results confirm that the homogeneous asymmetric hydrogenation by transition metal complexes is a viable method for obtaining quantities of both enantiomers of substituted glycerols which have a high value as synthetic precursors for the preparation of lipids and phospholipids. The compounds **5a** and **5b** in fact can be detritylated by standard methods to give the corresponding 1-O-octadecyl-sn-glycerol almost optically pure and 1-O-benzyl-sn-glycerol in high otical purity.

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8. **4a**:$^1$H NMR(80MHz,$CDCl_3$) δ : 7.6-7.2(m,15H),4.3(s,2H),3.9(s,2H),3.4(br.t, 2H),1.3(br.s ,32H),0.9(br.t,3H); m.p.= 53°C. **4b** :$^1$H NMR(80MHz,$CDCl_3$) δ : 7.6-7.1 (m,20H),4.5(s,2H),4.3(s,2H),3.9(s,2H); m.p.=85°C.

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11. $SiO_2$;hexane/ethylacetate 8/2. **5a** :$^1$H NMR(80MHz,$CDCl_3$) δ : 7.35(m,15H), 3.92 (m,1H),3.5(d,2H),3.45(t,2H),3.22(d,2H),2.25(s,1H,OH),1.3(s, 32H), 0.9(br.t,3H). **5b** :$^1$H NMR (80MHz,$CDCl_3$) δ : 7.6-7.2(20H),4.6(s,2H), 4.0(m,1H),3.6(d,2H) ,3.25 (d,2H), 2.45(s,1H,OH)

12. 1-O-octadecyl-3-O-trityl-glycerol(S)-(-)**5a** :$[\alpha]_D$-4.59°,(c=5,$C_6H_6$)(Lit.3 : $[\alpha]_D$ -4.78°);(R)-(+)**5a** :$[\alpha]_D$ +4.70°,(c=5,$C_6H_6$)(Lit.3 : $[\alpha]_D$ +4.72°, ref.3).1-O-benzyl-3-O-trityl-glycerol (S)-(-)**5b**:$[\alpha]_D$ -5.54°(c=5,$C_6H_6$) (Lit.3 :$[\alpha]_D$ -6.37°);(R)-(+)**5b**:$[\alpha]_D$ +5.59°(c=5,$C_6H_6$) (the specific rotation of(R)-(+)-**5b** is assumed to be equal but opposite to that of the optically pure (S)-(-)-5b , see ref.3).

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