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Synthesis of Asymmetric Propanetriol Analogues

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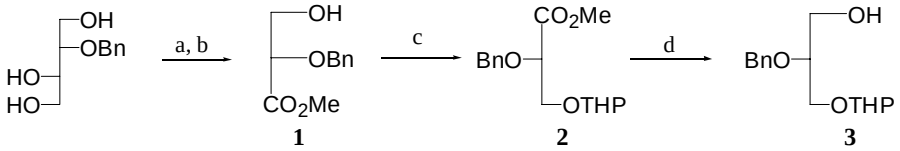
Abstract: From natural tartaric acid, (R)-2-benzyloxy-3-(2-tetrahydropyranyloxy) propanol **3** was designed and synthesized, and (R)-2-benzyloxy-3-(4-methoxybenzyloxy) propanol **7** was prepared in a new method. They can be used as chiral synthons of lysophosphatidic acid and other compounds with asymmetric propanetriol backbone.

Keywords: Chiral synthons, asymmetric propanetriol, synthesis.

The lysophosphatidic acid (LPA, 1-acyl-*sn*-glycerol-3-phosphate) level in plasma was directly associated with the ovarian cancer, patients suffering from which have significantly higher LPA level in plasma[1,2]. To develop a simple and sensitive immunological method of detecting LPA level (~μmol/L) is of significance in diagnosing ovarian cancer at early stage, and we tried to synthesize 1- (ω-amino) long-chained LPA and link it with protein to produce complete antigens. Two chiral synthons for this target compound, (R)-2-benzyloxy-3-(4-methoxybenzyloxy) propanol **7** and (R)-2-benzyloxy-3-(2-tetrahydropyranyloxy) propanol **3**, were designed and prepared *via* two routes respectively, as shown in **Scheme I** and **II**.

Scheme I



1 **2** **3**

So far there is no report about the synthesis of compound **3**. (S)-2-Benzyloxy-3-(2-tetrahydropyranyloxy) propanol was prepared from glycerol and followed enzymatic differentiation of the enantiotopic hydroxymethyl groups[3]. Compound **7** was synthesized from dibenzylated D-mannitol[4].

After 2S, 3S -3-benzyloxy-1, 2, 4-butanetriol (prepared from natural L-tartaric

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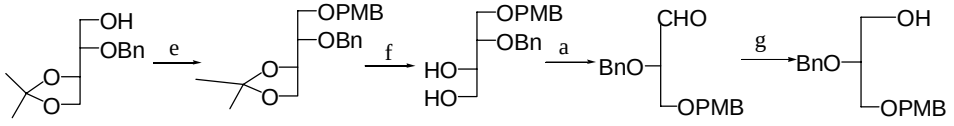
Scheme II



4 **5** **6** **7**

Reagents and conditions: a). $NaIO_4$/MeOH, rt.1.5 h. b). Br_2/MeOH, rt. 2 h; a, b overall yield 50%. c). DHP/PTSA/CH_2Cl_2, rt.3 h, 70%. d). $LiAlH_4$/THF, reflux 3.5 h, 78%. e). PMBCl/NaH/THF, reflux 11 h. f). 2 mol/L HCl/THF, rt. 6 h; e, f overall yield 60%. g). $NaBH_4$/MeOH, rt. 2 h; a, g overall yield 50%.

acid[5]) was successively oxidized by sodium periodate and bromine[6], the formed hydroxy ester **1**, which was protected by 3,4-dihydro-2*H*-pyran first, was reduced with lithium aluminiumhydride to produce compound **3** (**Scheme I**).

The adjacent two hydroxy groups of 2S, 3S-3-benzyloxy-1, 2, 4-butanetriol were protected by acetone[7] and the 4-hydroxy group was protected by 4-methoxybenzyloxy group to get compound **4**, which was hydrolyzed in acidic solution. Thus prepared butanediol **5** was oxidized by sodium periodate to obtain **6**, then **6** was reduced by sodium borohydride to get compound **7** (**Scheme II**).

Compounds **2, 3, 4, 5, 6** are all unreported (compounds **4** and **6** were not separated). The successful synthesis of compound **3** and **7** played an important role in our total synthesis of 1-(ω-amino long-chained acyl)-*sn*-glycerol-3-phosphate (ω-amino LPA).

Above all, two analogues of asymmetric propanetriol were prepared. Five compounds, **1, 2, 3, 5** and **7**, as showed in **Scheme I** and **II**, were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and HRMS.

The spectral data of chiral synthons **3** and **7** were shown in **Table 1**.

Table 1 The spectral data of compounds **3** and **7**

	3	**7**
$[\alpha]_D^{20}$	+3.5 (c 1.12, CH_3OH)	+19.3 （c 1.05， $CHCl_3$）
IR（film, ν,cm^{-1}）	3442.4,2923.4,1595.6,1408.9,1045.3	3438.9,2869.5,1610.9,1511.1,1457.6, 1248.3,1039.4,823.5,744.8
^{1}H NMR (200 MHz,$CDCl_3$, TMS, δ ppm)	7.35~7.37(m,5H,ArH);4.60~4.80(m,3H, PhCH_2,THPO);3.50~3.90(m,7H,CH, CH_2OH,CH_2OTHP,THPO);1.54~1.80 (m,7H,OH,THPO)	6.82~7.33(m,9H,ArH);4.47~4.74 (m,4H, *p*-MeOPhOCH_2,PhCH_2) ;3.59~3.80(m,8H, OCH_3,CH, CH_2OH,CH_2OPMB);2.30(br s,1H,OH)
^{13}C NMR (50 MHz,$CDCl_3$, TMS, δ ppm）	138.21, 128.36, 127.74, 127.71, 99.21, 99.04, 71.89, 67.09, 62.64, 30.45, 25.25, 19.42	158.75,138.00,129.68,128.89,127.95, 127.37,127.24,113.34,72.59,71.55,69.30, 62.01, 54.71,54.70
EIMS（*m/z*）	267(M+1), 235, 181, 134, 107	302(M,7%),211(28),181(24),137(43),121 (100),91(86)
HRMS（*m/z*）	($C_{15}H_{23}O_4$,M+1):calcd 267.1596, found 267.1588.	（$C_{18}H_{22}O_4$, M）: calcd 302.1518, found 302.1523

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