Stereospecific and regiospecific ring opening of glycidol with primary and secondary alcohols mediated by diisobutylaluminium hydride

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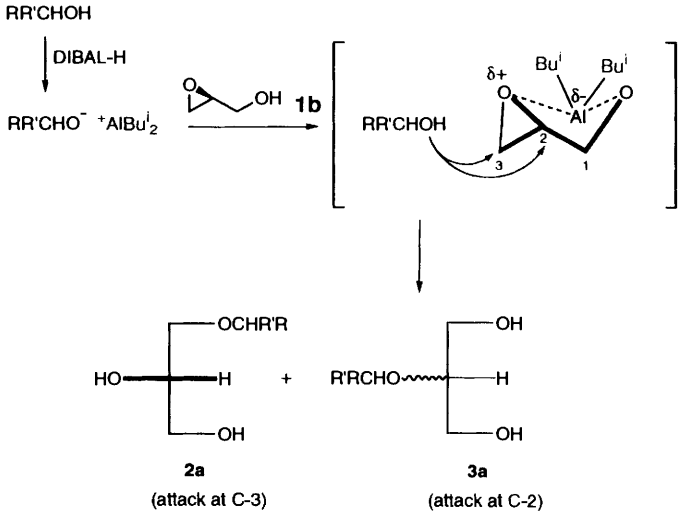
Regiospecific ring opening of (*R*)-(+)- or (*S*)-(−)-glycidol **1a, b** with primary and secondary alcohols in the presence of diisobutylaluminium hydride provides 1-*O*-alkyl-*sn*-glycerol **2** without formation of the undesired regioisomer, 2-*O*-alkylglycerol **3**. The configuration of the glycidol is preserved in the product.

Glycidol and its derivatives provide access to many important biological products.[1] Although regioselective ring-opening of glycidol at C-3 with amines, naphthols and thiols is well known,[1,2] only one report has appeared, to our knowledge, in which alcohols have been used to open underivatized glycidol. Most applications employ glycidol derivatives in which the primary hydroxy group is protected.[3] Johnson *et al.* have reported the synthesis of 1-*O*-alkyl-*sn*-glycerol by heating glycidol **1** with hexadecan-1-ol without solvent at 70–75 °C in the presence of $Ti(OC_{16}H_{33})_4$.[4] The limitations of this titanium-mediated nucleophilic opening reaction are: (a) use of a large excess (4 equiv.) of the alcohol; (b) formation of substantial amounts of by-product, 2-*O*-alkylglycerol; (c) the need to prepare the hexadecan-1-ol titanium (4+) salt; and (d) the requirement of sulfuric acid in the work-up to hydrolyse the titanium complex,[5] thus limiting the application of the reaction to water-insoluble 1-*O*-alkyl-*sn*-glycerols as the products.

As an extension of our interest in using glycerol derivatives as precursors of lipids,[6] we sought to use underivatized glycidol rather than *O*-protected glycidols as the C-3 synthon of ether-linked lipids, in order to minimize the use of protection and deprotection chemistry. Glycidol is prepared conveniently by catalytic asymmetric epoxidation[7] and is also available commercially in high optical purity. In this paper we report the first practical synthesis of 1-*O*-alkyl-*sn*-glycerol **2** from glycidol **1** mediated by diisobutylaluminium hydride (DIBAL-H), without producing the undesired regioisomer, 2-*O*-alkylglycerol **3**.† Advantages of the nucleophilic ring-opening of glycidol in the presence of DIBAL-H are: (i) secondary alcohols can be used as the nucleophile as well as primary alcohols with enantio- and regio-specificity; (ii) only 1.5 equiv. of the nucleophile (alcohol) are required; (iii) the undesired regioisomer **3** is not detected; and (iv) the work-up does not require acid hydrolysis. The regiospecific ring opening of (*S*)- or (*R*)-glycidol **1a, b** at C-3 mediated by DIBAL-H with nucleophiles such as primary alcohols and secondary alcohols is a useful and novel modification of the $Ti(OC_{16}H_{33})_4$-mediated opening reaction of glycidol. As shown in Table 1, the primary alcohols used were hexadecan-1-ol and octadecan-1-ol, and the secondary alcohols were hexadecan-2-ol, (±)-menthol and β-cholestanol. The yields obtained from the ring-opening reaction of glycidol with primary alcohols (48–50%) were higher than those with secondary alcohols (38–41%). The ring-opened diols **2** are important C-3 synthons in lipid chemistry.[3]



Scheme 1 The following RR'CHOH were used: hexadecan-2-ol, (±)-menthol and β-cholestanol. The long-chain primary alcohols with R = $C_{16}H_{33}$ or $C_{18}H_{37}$ and R' = H were also used.

A possible mechanistic rationale for the regiospecific DIBAL-H mediated opening involving complexation of glycidol in a four-co-ordinate Al derivative, activating the epoxide for C-3 attack of the alcohol, is shown in Scheme 1. Additional experiments are required to establish whether such co-ordination of the epoxy alcohol to the aluminium centre takes place.

In summary, the DIBAL-H mediated opening of (*R*)- or (*S*)-**1** reported in this communication is a convenient method for the synthesis of the enantiomers of alkyl lipids that are precursors of a variety of glycerolipids.

Experimental

Compounds **1a** and **1b** were obtained in 91 and 90% ee, respectively, from Aldrich Chemical Co.

General procedure for the preparation of 1-*O*-alkyl-*sn*-glycerol **2**. To a solution of the alcohol (1.5 equiv.) in dichloromethane was added DIBAL-H in toluene (1.3 equiv.) at 0 °C, and the reaction mixture was warmed to room temperature and stirred for 0.5 h. Glycidol (1.0 equiv.) was added to the reaction mixture which was then stirred at room temperature for 70 h. Potassium sodium tartrate (1.3 equiv.) in

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† Attempts to open **1** with hexadecan-1-ol in the presence of reagents other than DIBAL-H were unsuccessful; with magnesium alkoxide, BF_3·Et_2O and 9-BBN, product **2** was not obtained, polymer apparently being formed.

Table 1 Alcoholysis of underivatized glycidol mediated by DIBAL-H

Entry	Epoxide	RR'CHOH	Product **2a**/**3a**	t_R/min **2a** or **2b**	Yield[a] of **2a** or **2b**	% ee[b]
1	**1a**	$C_{16}H_{33}OH$	100[c]/0[d]	23.27	49	91
2	**1b**	$C_{16}H_{33}OH$	100/0	23.27	50	92
3	**1a**	$C_{18}H_{37}OH$	100/0	—	49	91
4	**1b**	$C_{18}H_{37}OH$	100/0	—	48	92
5	**1a**	$C_{14}H_{29}CH(CH_3)OH$	100[e]/0	22.38	41	90
6	**1b**	$C_{14}H_{29}CH(CH_3)OH$	100/0	22.38	40	90
7	**1a**	(±)-Menthol	100/0	14.35	39	—
8	**1a**	β-Cholestanol	—	*f*	38	—

[a] The percentage yield refers to the isolated yield. The structures of the products were confirmed by NMR and MS. [b] The % ee was determined by 400 MHz ^{1}H NMR of the crude bis(*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)-(−)-MTPA] esters (prepared according to ref. 8) derived from **2**. In each case baseline separation of the diastereoisomeric Mosher esters was achieved. [c] The isopropylidene derivatives of the diol **2** obtained from the reactions of **1** with hexadecan-1-ol and hexadecan-2-ol were made.[9] 2-*O*-Hexadecyl-*rac*-glycerol **3** was obtained from Serdary Research Labs. (London, Ontario) and converted into the corresponding 1,3-di-*O*-isopropylidene derivative. GC–MS analysis of the derivatized diols was carried out on a Hewlett-Packard 5988A GC-quadrupole mass spectrometer equipped with a H-P 1000 data system. Gas chromatography was carried out on a 30 m × 0.25 mm i.d., 0.25 μm DB-5 bonded phase fused silica capillary column (J & N Scientific, Folsom, CA). The injection temperature was 250 °C. The following program was used: initial temperature, 40 °C, 1 min; programmed at 20 °C min^{-1} to 100 °C; hold for 1 min; programmed at 10 °C min^{-1} to 250 °C; hold for 20 min. GC–MS analysis showed that the diols **2a**, **b** were free of the regioisomer. Helium carrier was used at a flow rate of 1 cm^3 min^{-1}. The retention times of 3-*O*-hexadecyl-1,2-isopropylidene-*sn*-glycerol and 2-*O*-hexadecyl-1,3-isopropylidene-*sn*-glycerol were 22.97 and 24.26 min, respectively. [d] The t_R of 2-hexadecylglycerol was 23.90 min. [e] Under the same conditions the t_R of the isopropylidene derivative of diol **2** obtained from the reaction of **1** with hexadecan-2-ol was 21.95 min and showed no trace of its regioisomer **3**. [f] The compound was decomposed on the GC column.

a minimum amount of water was then added to the mixture and stirring continued for 0.5 h. The mixture was extracted with ethyl acetate and the extract washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography to give 1-*O*-alkyl-*sn*-glycerol **2**. The GC retention times and % ee of the products were determined as described in the footnotes to Table 1.

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