A Convenient Synthesis of Long-Chain 1-O-Alkyl Glyceryl Ethers

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A convenient and economical procedure for synthesis of long-chain 1-O-alkyl glyceryl ethers (V) is described. Alkyl glycidyl ethers (II) which were derived from the reaction of alcohols (I) with epichlorohydrin using a phase transfer catalyst were first converted into the corresponding dioxolanes (III) or 1-O-alkyl-2,3-di-O-acetylglycerols (IV). Subsequent hydrolysis of the resultant products provided 1-O-alkyl glyceryl ethers (V) in high yields.

Long-chain 1-O-alkyl glyceryl ethers (V) and their derivatives are of considerable interest because of their pharmaceutical and physical properties (1-8). The most widely used methods for the synthesis of V are condensation of 1,2-O-isopropylideneglycerol with alkyl halides, tosylates or mesylates, followed by acid hydrolysis (9-12). Although these methods are useful and are used in laboratory synthesis, they are inconvenient in terms of time or expense, especially if large quantities are required.

In this paper we report our experiments on the convenient and economical preparation of V starting from alcohols I.

EXPERIMENTAL PROCEDURES

All the melting points are uncorrected. Infrared (IR) spectra were obtained with a Hitachi 260-50 IR spectrometer. ^1H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ using a Varian EM 360L NMR spectrometer. Chemical shifts were measured in ppm downfield from internal tetramethylsilane ($\delta=0$). The abbreviations "s, d, t and m" denote "singlet, doublet, triplet and multiplet," respectively.

Preparation of Alkyl Glycidyl Ethers (II): General procedure. To a vigorously stirred mixture comprising alcohol (I) (1.0 mol), 48% aqueous sodium hydroxide solution (3.0 mol as sodium hydroxide), quaternary ammonium salt (0.05 mol) and hexane (1000 ml), epichlo-

TABLE 1

Preparation of Oleyl Glycidyl Ether (IIf) in the Presence of Phase-Transfer Catalyst[a]

Phase-Transfer Catalyst	Yield (%)
$C_{10}H_{21}N^{\oplus}Me_3Cl^{\ominus}$	75
$C_{18}H_{37}N^{\oplus}Me_3Cl^{\ominus}$	72
$C_{18}H_{37}N^{\oplus}Me[(CH_2CH_2O)_4H]_2Cl^{\ominus}$	80
$Bu_4N^{\oplus}Br^{\ominus}$	82
$Bu_4N^{\oplus}HSO_4^{\ominus}$	84
$C_{12}H_{25}N^{\oplus}Me_2CH_2CO_2^{\ominus}$	75
$C_{18}H_{37}N^{\oplus}Me_2CH_2CO_2^{\ominus}$	60
Non-Catalyst	15

[a]If 0.1 mol, epichlorohydrin 0.2 mol, 48% NaOH 0.3 mol, phase-transfer catalyst 5 mol % (based on If), 50 C, 6 hr.

TABLE 2

Preparation of Glycidyl Ethers II

Product	R[a]	Catalyst[b]	Time (hr)	Yield (%)	b.p./mmHg (C)	Lit.[c] b.p. or molecular formula of new compounds[d]
IIa	n-C_6H_{13}[e]	A	5	75	72-74/5.0	98-99/20
IIb	n-$C_{12}H_{25}$	B	2	80	114-115/0.3	119-120/1.2
IIc	n-$C_{14}H_{29}$	F	5	86	120-125/0.15	174-176/3.0
IId	n-$C_{16}H_{33}$	B	3	82	123-125/0.1	169-172/1.8
IIe	n-$C_{18}H_{37}$	B	3	84	155-159/0.07	202-207/3.0
		C	6	72		
IIf	9-cis-$C_{18}H_{35}$	B	3	80	170-174/0.17	234-236/5.5
IIg	iso-$C_{18}H_{37}$	D	6	78	117-121/0.1	$C_{21}H_{42}O_2$ (326.5)
IIh	iso-$C_{18}H_{37}$	E	6	75	155-158/0.15	$C_{21}H_{42}O_2$ (326.5)
IIi	iso-$C_{18}H_{37}$	F	6	72	142-145/0.1	$C_{21}H_{42}O_2$ (326.5)

[a]Iso-$C_{18}H_{37}$ are as follows: g, 5,7,7-trimethyl-2-(1,3,3-trimethylbutyl)octyl; h, 2-heptyl undecyl; i, 2-methyl heptadecyl.

[b]A, $C_{12}H_{25}N^{\oplus}Me_3Cl^{\ominus}$; B, $C_{18}H_{37}N^{\oplus}Me[(CH_2CH_2O)_4H]_2Cl^{\ominus}$; C, $C_{18}H_{37}N^{\oplus}Me_3Cl^{\ominus}$; D, $C_{10}H_{21}N^{\oplus}Me_3Cl^{\ominus}$; E, $(C_8H_{17})_3N^{\oplus}MeCl^{\ominus}$; F, $Bu_4N^{\oplus}HSO_4^{\ominus}$.

[c]The known compounds (**IIa-IIf**) were identified by comparison of their spectral data with those of authentic samples (20).

[d]The microanalyses were in satisfactory agreement with the calculated values: C, ± 0.25; H, ± 0.30.

[e]The reaction was carried out at 20 C.

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TABLE 3

Preparation of Dioxolanes III

Product	Yield (%)	b.p./mmHg (C)	Molecular formula[a]	IR(cm^{-1}, neat)	^{1}H-NMR($CDCl_3$) δ[ppm] R′	-$CH_2OCH_2CHCH_2$-
IIIb[b]	90	138-142/0.40	$C_{18}H_{36}O_3$ (300.4)	1380, 1370, 1255, 1210, 1105, 1055, 845, 720	0.83 (t, 3H), 1.25 (m, 20H) 1.34 (s. 3H), 1.40 (s, 3H)	3.25-4.25 (m, 7H)
IIIc[b]	92	162-165/0.50	$C_{20}H_{40}O_3$ (328.6)	1380, 1370, 1260, 1210, 1115, 1050, 845, 720	0.86 (t, 3H), 1.27 (m, 24H) 1.33 (s, 3H), 1.39 (s, 3H)	3.30-4.40 (m, 7H)
IIId[b]	88	175-177/0.50	$C_{22}H_{44}O_3$ (356.6)	1380, 1370, 1260, 1240, 1215, 1120, 1080, 1060, 850, 720	0.85 (t, 3H), 1.27 (m, 28H) 1.36 (s, 3H), 1.39 (s, 3H)	3.20-4.30 (m, 7H)
IIIe[c]	90	178-182/0.07	$C_{24}H_{48}O_3$ (384.6)	1380, 1370, 1255, 1210, 1110, 1050, 840, 720	0.80 (t, 3H), 1.23 (m, 32H) 1.33 (s, 3H), 1.39 (s, 3H)	3.30-4.40 (m, 7H)
IIIf[d]	90	173-176/0.07	$C_{24}H_{46}O_3$ (382.6)	1380, 1370, 1260, 1215, 1120, 1080, 1060, 850, 720	0.87 (t, 3H), 1.25 (m, 24H) 1.34 (s, 3H), 1.40 (s, 3H) 1.70-2.30 (m, 4H), 5.25 (t, 2H)	3.20-4.30 (m, 7H)
IIIg	90	142-143/0.15	$C_{24}H_{48}O_3$ (384.6)	1390, 1380, 1365, 1250, 1210, 1150, 1110, 1050, 850	0.90 (s, 18H), 0.85 (m, 6H) 1.0-1.35 (m, 11H) 1.35 (s, 3H), 1.40 (s, 3H)	3.20-4.40 (m, 7H)
IIIh	90	165-168/0.15	$C_{24}H_{48}O_3$ (384.6)	1380, 1370, 1255, 1210, 1150, 1110, 1070, 1050, 845, 720	0.89 (t, 6H), 1.29 (m, 29H) 1.35 (s, 3H), 1.41 (s, 3H)	3.25-4.40 (m, 7H)
IIIi	88	200-203/1.2	$C_{24}H_{48}O_3$ (384.6)	1370, 1355, 1240, 1200 1080, 1040, 830, 710	0.86 (t, 3H), 0.90 (d, 3H) 1.28, (m, 29H), 1.35 (s, 3H) 1.40 (s, 3H)	3.20-4.50 (m, 7H)

[a]The microanalyses were in satisfactory agreement with the calculated values: C, ± 0.24; H, ± 0.20.

[b]Reference (22).

[c]Reference (5).

[d]Reference (6).

rohydrin (2.0 mol) was added drop by drop for 30 min at room temperature. After completion of the addition of epichlorohydrin the mixture was stirred vigorously at 20-50 C for 2-6 hr. The reaction mixture was cooled, and the organic layer was separated. The solvent was evaporated from the organic layer under reduced pressure and the residue distilled in vacuo to give II (Tables 1 and 2).

Preparation of 1-O-Alkyl Glyceryl Ethers (V): General Procedure. Method A: To a mixture of acetone (12 mol) and boron trifluoride etherate (0.05 mol), glycidyl ether II (1 mol) was added gradually over a period of one hr at room temperature. The resultant solution was stirred for an additional two hr and treated with powdered sodium bicarbonate (0.1 mol). Excess acetone was removed at 60-80 C and the residue treated with 600 ml of water at room temperature. The organic layer was then distilled under reduced pressure to give dioxolane III as a colorless oil (Table 3).

A mixture consisting of thus obtained dioxolane III (1.0 mol), concentrated sulfuric acid (0.05 mol), methanol (500 ml) and water (500 ml) was heated under reflux with vigorous stirring for several hours. The resultant mixture was cooled to 50 C and neutralized

TABLE 4

Preparation of 1-O-Alkyl-2,3-di-O-acetylglycerols IV

$R'CH_2OCH_2\overset{\beta}{C}HCH_2OAc$

OAc

Product	Catalyst[a]	Yield (%)	b.p./mmHg (C)	Molecular formula[b]	IR (cm^{-1}, neat)	^{1}H-NMR($CDCl_3$)δ[ppm] R′	R′CH_2O	Hα	Hβ	Hγ	OAc
IVa[c]	A	95	128-130/1.8	$C_{13}H_{24}O_5$ (260.3)	1740, 1370, 1220 1110, 1040, 955	0.85 (t, 3H) 1.33 (m, 8H)	3.44 (t, 2H)	3.50 (d, 2H)	5.18 (m, 1H)	3.85-4.50 (m, 2H)	2.08 (s, 6H)
IVb	B	90	164-168/0.7	$C_{19}H_{36}O_5$ (344.5)	1740, 1370, 1240 1220, 1110, 1050 955	0.85 (t, 3H) 1.28 (m, 20H)	3.40 (t, 2H)	3.50 (d, 2H)	5.15 (m, 1H)	3.90-4.50 (m, 2H)	2.01 (s, 6H)
IVf[d]	B	95	224-228/0.5	$C_{25}H_{46}O_5$ (426.6)	1740, 1360, 1220 1110, 1040, 955	0.87 (t, 3H) 1.33 (m, 24H) 2.00 (m, 4H) 5.33 (t, 2H)	3.45 (t, 2H)	3.52 (d, 2H)	5.20 (m, 1H)	3.90-4.60 (m, 2H)	2.10 (s, 6H)

[a]A, Et_3N; B, $Me_2N(CH_2)_6NMe_2$.

[b]The microanalyses were in satisfactory agreement with the calculated values: C, ± 0.25; H, ± 0.28.

[c]Reference (24).

[d]Reference (6).

TABLE 5

Preparation of 1-O-Alkyl Glyceryl Ethers V

Product	Method	Yield[a] (%)	m.p. or b.p./mmHg	Lit[b] m.p. or molecular formula[c]	^{1}H-NMR ($CDCl_3$) δ[ppm]
Va[d]	B	90	112-115/0.6	$C_9H_{20}O_3$ (176.3)	0.88 (t, 3H), 1.33 (m, 8H), 3.1-4.0 (m, 9H)
Vb	A	88	49	49.5	
	B	87			
Vc	A	90	58	58.5	
Vd	A	86	65	65.5	
Ve	A	87	70.5	71-71.5	
Vf	A	88	18.5	18-19	
	B	93			
Vg	A	88	liquid	$C_{21}H_{44}O_3$(344.6)	0.83 (s, 18H), 1.0-1.5 (m, 17H), 3.25-4.0 (m, 9H)
Vh	A	87	liquid	$C_{21}H_{44}O_3$(344.6)	0.83 (t, 6H), 1.25 (m, 29H), 3.2-4.2 (m, 9H)
Vi	A	86	37-38	$C_{21}H_{44}O_3$(344.6)	0.85 (t, 3H), 0.91 (d, 3H), 1.28 (m, 29H), 3.25-4.25 (m, 9H)

[a]Yields are based on glycidyl ethers *II*.

[b]Reference (9).

[c]The microanalyses were in satisfactory agreement with the calculated values: C, ± 0.21; H, ± 0.31.

[d]Reference (24).

with a diluted sodium hydroxide solution. The oily organic mass was separated and dried under reduced pressure at 80-90 C for a few hours to give V. Recrystallization or column chromatography (silica gel column with ethyl acetate as an eluent) gave an analytically pure sample (Table 5).

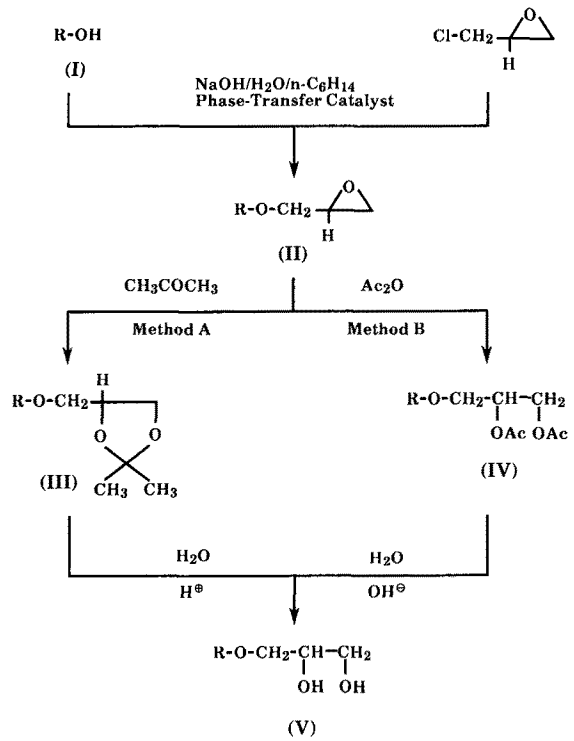
Method B: To a stirred mixture of acetic anhydride (5.0 mol) and tertiary amine (0.05 mol), glycidyl ether II (1.0 mol) was added over one hr at 100-120 C. The mixture was stirred for an additional three hr at this temperature. The excess acetic anhydride was removed under reduced pressure and the residue neutralized with a dilute hydrochloric acid solution. The organic layer was separated and distilled under reduced pressure to give 1-O-alkyl-2,3-di-O-acetylglycerol (**IV**) as a colorless oil (Table 4).

To a stirred mixture of 30% aqueous sodium hydroxide solution (2.5 mol as sodium hydroxide) and ethanol (500 ml), thus obtained **IV** (1.0 mol) was added drop by drop at room temperature. After heating the mixture under reflux for several hours, it was cooled to room temperature and neutralized with a 0.5N hydrochloric acid solution. Ether (500 ml) was added and the organic layer separated. After evaporation of the solvent from the organic layer, the oily organic mass was dried under reduced pressure to yield **V** (Table 5).

RESULTS AND DISCUSSION

Our improved methods (A and B) for the synthesis of long-chain 1-O-alkyl glyceryl ethers (**V**) are outlined in Scheme 1. An essential feature in these routes is the utilization of alkyl glycidyl ethers II as key intermediates and their transformation into the corresponding dioxolanes **III** or 1-O-alkyl-2,3-di-O-acetylglycerols (**IV**).

In the course of our studies, it has been reported (13-15) that some glycidyl ethers can be obtained from the reaction of alcohols with epichlorohydrin using a phase transfer catalyst (PTC) (16-19). However, the reactions of fatty alcohols **I** have not been widely investigated. We examined the reaction of oleyl alcohol (**If**) with epichlorohydrin in the presence of various kinds of quaternary ammonium salts to see the effect of structure of catalysts on the yield of the corresponding glycidyl ether **IIf**. The results are summarized in



SCHEME 1.

Table 1. The yield was not markedly affected by the counter-ion or the chain length of quaternary ammonium catalysts. It was found to be convenient to carry out the reaction in hexane. Optimum PTC conditions were realized when the two phase system consisting of **If** (1 mol equiv), hexane, 48% aqueous sodium hydroxide (3 mol equiv), epichlorohydrin (2 mol equiv) and quaternary ammonium salts (5 mol%) were stirred at 50 C.

The present reaction can be applied to a variety of straight or branched long-chain alcohols. The corresponding glycidyl ethers **II** were obtained in reasonable yields as shown in Table 2.

Although glyceryl ethers **V** are generally obtainable by direct ring-opening of **II** with water or addition of acids to **II** followed by hydrolysis, these reactions involve various side reactions and polymer formation, especially in the preparation of long-chain alkyl glyceryl ethers **V**. The isolation of **V** is usually very difficult. We found that **V** can be conveniently obtained in high yields by converting **II** into the corresponding dioxolanes **III** or 1-O-alkyl-2,3-di-O-acetylglycerols (**IV**), followed by hydrolysis.

Glycidyl ethers **II** were thus converted into dioxolanes **III** by the reaction with acetone in the presence of a catalytic amount of boron trifluoride etherate ($BF_3 \cdot áOEt_2$), as reported for the lower alkyl glycidyl ethers (21). The structures of **III** were established on the basis of elemental, NMR and IR spectral analyses and comparison with an authentic specimen. The yields and the spectral data for the newly synthesized dioxolane derivatives **III** are listed in Table 3.

Finally, **III** were treated with concentrated mineral acid giving the corresponding 1-O-alkylglyceryl ethers **V** (Table 5) in almost quantitative yields (Method A).

On the other hand, 1-O-alkyl-2,3-di-O-acetylglycerols (**IV**) (Table 4), derived from the addition of acetic anhydride to glycidyl ethers **II** in the presence of a catalytic amount of tertiary amine (23), afforded **V** after alkaline hydrolysis (Method B) in almost the same yields as in Method A.

Thus, we have found that long-chain alkyl glyceryl ethers **V** can be prepared from alcohols **I** through the corresponding dioxolanes **III** or 1-O-alkyl-2,3-di-O-acetylglycerols (**IV**) in moderate to high yields (62-77% overall yields based on **I**). That the reaction requires no special conditions or expensive reagents may make these two procedures methods of choice for the large scale preparation of **V**.

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[Received July 20, 1987;
accepted April 6, 1988]