A Facile Route for Synthesis of Long-Chain *rac*-1-S-Alkylglycerols

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Alkyl allyl thioethers were prepared by reaction of long-chain primary thiols in hexane with allyl bromide in the presence of a phase transfer catalyst (tetrabutylammonium bromide), and aqueous alkali and were hydroxylated to *rac*-1-S-alkylglycerols by means of a novel reagent, cetyltrimethylammonium permanganate, in dichloromethane.

KEY WORDS: Alkyl allyl thioethers, hydroxylation, *rac*-1-S-alkylglycerols.

1-S-Alkylglycerols constitute valuable starting materials for the synthesis of complex lipids that exhibit biological activity (1). These compounds are also useful as model substances in biochemical and biomedical applications (2). Thioether lipids containing a long-chain alkyl moiety are found in human and marine animal tissues in small quantities (3,4). The thioether lipids occurring in mammalian hearts consist mainly of components with saturated 1-S-alkyl groups of 12-18 carbons (5,6). An earlier synthetic method involved the *in situ* preparation of potassium mercaptide of 1-thioglycerol and subsequent alkylation by the appropriate long-chain alkyl bromide or iodide to give the required 1-S-alkylglycerol (7). The present communication reports a new route for synthesis of saturated *rac*-1-S-alkylglycerols, which involves the preparation of alkyl allyl thioethers from long-chain primary thiols and allyl bromide in the presence of the phase transfer catalyst, tetrabutylammonium bromide (TBAB), and subsequent hydroxylation (8) of the thioether with the novel hydroxylation reagent cetyltrimethylammonium permanganate (CTAP) in dichloromethane (DCM) to yield *rac*-1-S-alkylglycerols.

MATERIALS AND METHODS

Melting points were determined on a Mettler FP 51 instrument (Mettler Instrument AG, Zürich, Switzerland) and are uncorrected. Microanalyses were carried out with a CHN-600 analyzer (Leco Corp., St. Joseph, MI). Infrared (IR) spectra were obtained with a Perkin-Elmer Model 283 B spectrophotometer (Perkin-Elmer, Norwalk, CT). Proton nuclear magnetic resonance (NMR) spectra were obtained with a JEOL FX 90 Q instrument. Chemical shifts were measured in ppm downfield from internal tetramethylsilane (δ=0). Mass (MS) spectra were obtained in a V.G. Micromass 7070 H mass spectrometer (V.G. Analytical Ltd., Manchester, England). Gas-liquid chromatography (GLC) was carried out in a Tracor 540 gas chromatograph (Tracor Instruments, Austin, TX) fitted with a glass column (6′ × 1/8″) containing 5% SE-30, a hydrogen flame ionization detector and a personal computer. The column, injection port and detector temperatures were maintained at 210, 250 and 300°C, respectively. Flow rate of carrier gas (nitrogen) was 18 psig. Allyl bromide and TBAB of 96% purity were purchased from Aldrich Chemical Company (Milwaukee, WI). The long-chain primary thiols of >95% purity were purchased from Fluka Chemie (Buchs, Switzerland). Reagent-quality solvents were used without further purification.

Allyl decyl thioether (II a): Typical procedure. To a vigorously stirred mixture of 1-decane thiol (I a; 50 mM), 48% aq. NaOH (150 mM), TBAB (2.5 mM) and hexane (60 mL), allyl bromide (66 mM) was added dropwise for 30 min at 25–30°C. Then the mixture was stirred vigorously at 45°C for 1 hr and cooled to 30°C. The organic layer was separated and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was distilled *in vacuo* to yield allyl decyl thioether (Table 1). IR (neat, cm^{-1}): 3065, 1645, 980, 905. ^1H NMR ($CDCl_3$, δ): 6.06-5.56 m (1H, -C<u>H</u>=), 5.30-4.95 m (2H, $=CH_2$), 3.11 d (2H,-S-C<u>H</u>$_2$-C=C), 2.44 t [2H, -$(CH_2)_8$-C<u>H</u>$_2$-S-], 1.27 br s [16H,-$(C\underline{H}_2)_8$-], 0.89 t (3H, -C<u>H</u>$_3$). Mass *m/z* (relative intensity, %): 214 ($M^{+\cdot}$, 18.0), 174 ($C_{10}H_{22}S^{+\cdot}$, 13.1), 173 ($C_{10}H_{21}S^+$, 100), 87 (CH_2=S-CH_2-CH=CH_2, 14.8), 74 (CH_2=CH-CH_2-$HS^{+\cdot}$, 34.3), 41 ($C_3H_5^+$, 9.8).

TABLE 1

Physical and Microanalytical Data of Alkyl Allyl Thioethers

Product	Yield[a] (%)	B.P. (°C/mmHg) or M.P. (°C)	Molecular formula (Mol. wt.)	Microanalysis Calculated C	Calculated H	Found C	Found H
Decyl allyl thioether (II a)	95	90-92/4.5	$C_{13}H_{26}S$ (214.4)	72.9	12.1	72.6	12.3
Dodecyl allyl thioether (II b)	94	140-150/3.0	$C_{15}H_{30}S$ (242.5)	74.4	12.4	74.7	12.6
Hexadecyl allyl thioether (II c)	97	190-198/5.0	$C_{19}H_{38}S$ (298.6)	76.5	12.8	76.2	13.0
Octadecyl allyl thioether (II d)	95	25-26	$C_{21}H_{42}S$ (326.6)	77.3	12.9	77.2	13.1

[a]Yields are for distilled materials and are based on alkyl thiols.

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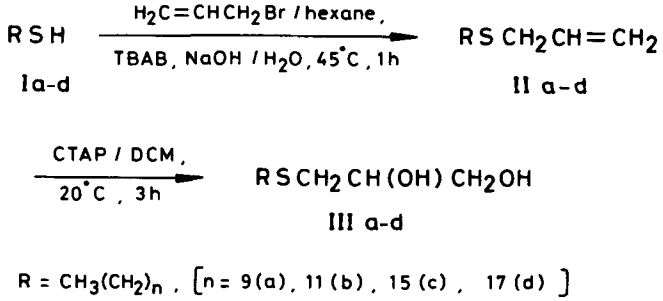
TABLE 2

Physical Data of *rac*-1-S-Alkylglycerols

Product	Yield[a] (%)	M.P. (°C)	Lit. m.p. (°C)
rac-1-S-Decylglycerol (III a)	64	43-44	44-45
rac-1-S-Dodecylglycerol (III b)	63	50-51	50-51
rac-1-S-Hexadecylglycerol (III c)	60	65-66	68-70[b]
rac-1-S-Octadecylglycerol (III d)	60	74-75	74-75

[a]Yields are for isolated products and are based on alkyl allyl thioethers.

[b]Reference 9.



SCHEME 1. Synthesis of *rac*-1-S-alkylglycerols. TBAB, tetrabutyl ammonium bromide; CTAP, cetyl trimethyl ammonium permanganate; and DCM, dichloromethane.

rac-1-S-Decylglycerol (III a): Typical procedure. CTAP (6.5 mM) in DCM (30 mL) was added dropwise to allyl decyl thioether (5 mM) in DCM (15 mL) at 20°C. Stirring was continued for 3 hr and the mixture was concentrated to half of its volume. The residual solution was diluted with diethylether (100 mL) and filtered through a pad of celite and anhydrous sodium sulfate. The filtrate was evaporated under reduced pressure and the product was purified by silica gel column chromatography. Unconverted allyl decyl thioether was eluted with n-hexane/diethylether (90:10, v/v). *rac*-1-S-Decylglycerol (Table 2) was eluted with ethyl acetate and further purified by recrystallization from ethyl acetate. IR (KBr, cm^{-1}): 3510-3000. ^1H NMR ($CDCl_3$, δ): 3.94-3.43 m [3H, C<u>H</u>(OH)-C<u>H</u>$_2$OH], 2.89-2.38 m (4H, -CH_2-S-CH_2-), 1.59 s 2H, D_2O exchangeable), 1.27 br s [16H, -$(CH_2)_8$-], 0.89 t (3H, -CH_3). Mass *m/z* (relative intensity, %): 248 ($M^{\cdot+}$, 4.1), 230 (M-18, 9.0), 217 (M-31, 9.8), 187 ($C_{10}H_{21}$-$\overset{+}{S}$=CH_2, 8.2, 174 ($C_{10}H_{22}S^{+\cdot}$, 23.0), 173 ($C_{10}H_{21}S^+$, 21.3), 140 (M-108, 44.3), 61 ($C_2H_5S^+$, 67.2), 43 ($C_3H^{+\cdot}$, 100).

RESULTS AND DISCUSSION

The present route of synthesis of long-chain *rac*-1-S-alkylglycerols is outlined in Scheme 1. Allyl decyl, allyl dodecyl, allyl hexadecyl and allyl octadecyl thioethers were prepared by reaction of long-chain primary thiols in hexane with allyl bromide in the presence of TBAB at 45°C for 1 hr. The conversion of thiols is almost quantitative after 1-hr reaction time. The course of formation of alkyl allyl thioethers was followed by GLC on a glass column containing SE-30, which separated the thiols from the respective alkyl allyl thioethers. For example, the relative retention time of allyl dodecyl thioether was 2.03, with respect to dodecane thiol (1.0). The homologous alkyl allyl thioethers were also separated similarly. The relative retention times were 0.55, 3.61 and 6.94 for decyl, hexadecyl and octadecyl allyl thioethers, respectively, with respect to dodecyl allyl thioether (1.0). The alkyl allyl thioethers were distilled (Table 1) under reduced pressure to get pure products. The IR spectra of alkyl allyl thioethers showed strong bands at 905 and 980 cm^{-1} due to CH_2 and CH out-of-plane deformation vibration of the terminal double bond. The IR spectra also showed bands at 3065 and 1645 cm^{-1} due to CH and C=C stretching vibrations of the double bond. The mass spectra of alkyl allyl thioethers showed a clear molecular ion peak. For all compounds the base peak is obtained by the loss of allyl radical from the molecular ion. The NMR spectra of alkyl allyl thioethers showed two multiplets at 5.6-6.1 δ, accounting for one proton assignable to =CH, and at 4.9-5.3 δ, accounting for two protons assignable to =CH_2. A doublet at 3.1 δ, accounting for two protons, is due to the methylene group flanked by sulfur and the terminal double bond. A triplet at 2.4 δ, accounting for two protons, is due to the methylene group flanked by sulfur and the long-chain alkyl group. In addition to the above, a broad singlet at 1.3 δ and a triplet at 0.9 δ represent the long-chain methylene and terminal methyl groups, respectively.

The alkyl allyl thioethers (II a-d) were hydroxylated with the novel hydroxylation reagent CTAP in DCM to get *rac*-1-S-alkylglycerols (Table 2). The *rac*-1-S-alkylglycerols were purified by silica gel column chromatography. The structures of the alkyl glycerols were established on the basis of their IR, NMR and MS data and by comparison of their melting points with the literature values (Table 2). A little variation was found in the melting point of *rac*-1-S-hexadecylglycerol as compared to the literature value. The IR spectra of *rac*-1-S-alkylglycerols (III a-d) showed the characteristic band at 3500-3100 cm^{-1} due to OH stretching vibrations. The NMR spectra showed two multiplets at 2.4-2.9 and 3.4-3.9 δ, accounting for four protons and three protons assignable to protons of the two methylene groups attached to sulfur and of CH and CH_2 attached to the two hydroxy groups, respectively. The NMR spectra also showed D_2O-exchangeable protons as a sharp singlet at 1.6 δ. In addition to the above, the NMR spectra of alkylglycerols also showed a broad singlet at 1.3 δ and a triplet at 0.9 δ for the multiple methylene and terminal methyl groups, respectively. The mass spectra of *rac*-1-S-alkylglycerols showed a less intense molecular ion peak and prominent peaks corresponding to M-18, M-31, M-61 and M-74. Formation of a peak due to the loss of a 108 fragment from the molecular ion is observed in all the spectra of *rac*-1-S-alkylglycerols. This could perhaps be attributed to a heterolytic cleavage between sulfur and carbon, and a subsequent transfer of hydrogen from the long-chain alkyl moiety, leaving a positive charge on the alkyl fragment.

In the present route, use of alkyl thiols and allyl bromide in the mole ratio of 1:1.3 resulted in quantitative conversion of alkyl thiols to alkyl allyl thioethers in yields ranging from 94-97% of the distilled products. The preparation of the hydroxylation reagent does not require special chemicals and precautions. The hydroxylation step is mild and the reaction product needs a simple work-up to get the *rac*-1-S-alkylglycerols in good yields (60-64%).

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