

Regioselective and stereospecific cleavage of a terminal oxirane system: A novel synthetic approach to lipid mediator congeners—1,2(2,3)-diacyl-3(1)-halo-*sn*-glycerols

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Received 14 March 2006; revised 4 April 2006; accepted 5 April 2006

Available online 3 May 2006

Abstract—Glycidyl esters upon treatment with a mixture of carboxylic acid anhydride (CAA) and trimethylsilyl halide (TMSX) in the presence of tetra-*n*-butylammonium halide (Bu₄NX, X = Cl, Br or I) undergo stereospecific and regioselective opening of the oxirane ring to afford mixed-(or mono)-acid 1,2(2,3)-diacyl-3(1)-halo-*sn*-glycerols in high yields.
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Importance of stereochemically pure glycerolipids as components of biological membranes and physiological effectors^{1–4} constitutes a strong justification for using these compounds and their conjugates in carbohydrate research,^{5,6} physiology,^{7,8} membranology,⁹ enzymology,^{10–12} and in rational drug design.^{13–16}

Valuable synthetic precursors for the preparation of mono-, di-, and triglycerides, and their analogues with defined stereochemistry are 1,2(2,3)-diacyl-3(1)-halo-*sn*-glycerols bearing two acyl moieties in a three-carbon skeleton. Unfortunately, classical strategies to this class of compounds that involve lengthy multistep functionalization of glycerol starting materials^{1,2,15,17} are usually low yielding and require painstaking chromatographic separations of the isomeric compounds or by-products at each synthetic stage.

Oxirane derivatives, while finding numerous applications as versatile synthons in organic synthesis,^{18,19} have not been exploited to any significant extent for accessing such diester C3-building blocks. This is probably due to the fact that direct cleavage of terminal epoxides having even a rigid allylic substituent (e.g., alkyl, aryl or ether-derived moieties) with acyl chlorides (e.g., alone,²⁰ in the presence of CrO₂Cl₂,^{21,22} CoCl₂,²³ Bu₂SnCl₂/Ph₃P,²⁴ or

hexaalkylguanidinium chloride²⁵) or parent haloacylating agents (e.g., TiCl₄/EtOAc/imidazole²⁶) is often limited by competing rearrangements or incompatibility with oxidation-/Lewis acid-sensitive substrates,¹⁷ and affords only low reactive *O*-acylated vicinal chlorohydrins. An alternative two-step protocol, comprising a SnX₂-assisted fission of the oxirane ring with trimethylsilyl halide (TMSX) followed by acylation of the produced halohydrin,²⁷ suffers from erratic yields and extensive acyl migration.

Finally, acyl bromides alone²⁸ or as in a most recent variant of this method, in which a bromoacylating species was generated in situ from either LiBr-carboxylic acid anhydrides⁴ or LiBr-oleic anhydride-benzyltributylammonium bromide,²⁹ has been advocated as method of choice for haloacylation of glycidyl esters without acyl migration. The approach, however, seems to be restricted to the synthesis of the bromo derivatives, and the reaction conditions do not prevent complete formation of isomeric products.²⁹

Recently, as part of our program on new synthetic strategies for glycerolipids,^{30–32} we developed a three-component system: Bu₄NBr-TMSBr-carboxylic acid anhydrides (CAA), that efficiently eliminated a perennial problem of diglyceride chemistry, namely, an acyl migration, by a direct replacement of an *O*-silyl moiety by an acyl group without exposure of a free hydroxyl function.³³

Keywords: Lipid mediator; Glycidol; Diacylglycerols.

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Herein, we report that the same type of a reagent system, that is, CAA-TMSX-Bu₄NX (X = Cl, Br or I), when applied to oxirane derivatives, effects a regioselective haloacylating ring cleavage of glycidyl esters to produce under mild conditions configurationally homogeneous mixed-acid (or mono-acid) 2-*O*-acylated vicinal chloro-, bromo-, or iodohydrins of glycerol in high isolated yields.

To assess efficacy of this new protocol for a direct conversion of glycidyl esters into the corresponding vicinal haloesters (Scheme 1), the reaction of representative glycidyl oleates **1** and **2** was investigated by varying the experimental conditions (solvents, ratio of reactants, etc.).

The best results were obtained when a solution of test substrate **1** or **2** and Bu₄NX (2.0 equiv) in chloroform was treated in a tightly stoppered pressure flask at 80 °C with a mixture of a carboxylic acid anhydride (3.0 equiv) and TMSX (1.3 equiv) for 30 min to 5 h. This produced quantitatively and in a highly chemo- and regioselective manner (>99%, ¹H and ¹³C NMR spectroscopy) the expected acylated halohydrin derivatives **3–7**, which were isolated in 90–94% yields after flash column silica gel chromatography.³⁴ No by-products due to possible acyl migration or attack of a carboxylate on the terminal halo-center, as well as side reactions involving the native olefinic part of oleic acid residue, could be detected by TLC and ¹H/¹³C NMR spectral analysis. In all instances, rate of the process was not appreciably affected by structural or electronic features of the glycidyl derivatives (e.g., acetyl, oleoyl or benzoyl; results not shown), but it was sensitive to the nature of halogen in the quaternary ammonium salts, increasing abruptly from chloride to iodide. The reaction seemed to be rather general as other glycidol conjugates (e.g., linoleoyl, stearoyl, hexadecyl, or isopropyl; data not shown) also underwent practically quantitative conversion to the corresponding 2-*O*-acylated vicinal halohydrins.

Since treatment of the carboxylic acid anhydrides at room temperature with TMSX (1.0 equiv) alone, or in the presence of 2.0–4.0 equiv of Bu₄NX (e.g., X = Br, or I), led to almost instantaneous production of equimolar amounts of the corresponding acyl halides (AcX) and trimethylsilyl esters (AcTMS),³³ mechanistic

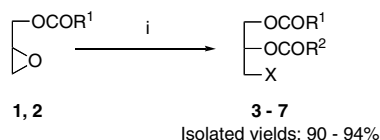
contribution of these species to the haloacylating fission of the oxirane ring was examined next.

Model experiments (in CHCl₃/80 °C/1–6 h/pressure tube) supported by ¹H and ¹³C NMR spectroscopy showed that acetyl bromide (1.5 equiv) by itself or in combination with acetic anhydride (6.0 equiv), in the presence or absence of trimethylsilyl acetate (3.0 equiv), effected cleavage of glycidyl oleate **1** with a predominant migration of the oleoyl moiety yielding 1-acetyl-2-oleoyl-3-bromoglycerol and 1-oleoyl-2-acetyl-3-bromoglycerol in an approximate ratio of 85:15. The use of acetic anhydride (6.0 equiv) along with TMSBr (1.5 equiv) gave analogous results, while replacement of TMSBr by Bu₄NBr (4.0 equiv) resulted in a mixture consisting of unreacted epoxide **1** (~50%), the target 1-oleoyl-2-acetyl-3-bromoglycerol (~30%), and 1-oleoyl-2,3-bis(acetylated) glycerol (~20%).

By contrast, haloacetylation of **1** with acetyl bromide (1.3 equiv) in the presence of Bu₄NBr (2.0 equiv) afforded the expected 1-oleoyl-2-acetyl-3-bromoglycerol regioselectively, but this also produced certain amounts of 2-oleoyl-1,3-bromoglycerol (~5%). As expected, quaternary ammonium salts (Q⁺X[−]) catalyzed a halide ion exchange with AcX as evidenced by formation of both 1-oleoyl-2-acetyl-3-iodoglycerol and 1-oleoyl-2-acetyl-3-chloroglycerol in a ratio of 1:2, respectively, upon treatment of **1** with AcCl (1.3 equiv) in the presence of Bu₄NI (4.0 equiv).

The above observations are consistent with a mechanism which involves a nucleophilic attack of a halide ion on the oxirane system, which is activated by AcX as depicted in Scheme 2.

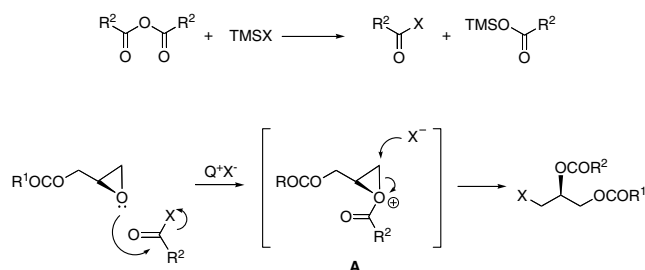
As an acyl halide, generated in situ from CAA and TMSX, is expected to be a strong electrophile catalyst that can coordinate to the epoxide oxygen forming an intermediate of type **A**, these two steps, electrophilic catalysis and the nucleophilic opening of the epoxide system, are likely to be synchronous. This rationalizes the fact that acylated halohydrins **3–7** are formed without an adjacent acyl group migration, and since no C–O bond breaking takes place at the chiral center of the glycidol, the transformation should be stereospecific and occur with retention of configuration. In the absence of carboxylic anhydrides and trimethylsilyl ha-



- 1** = *S*-(+), R¹ = C₁₇H₃₃ **3** = 3-halo-*sn*, R¹ = C₁₇H₃₃, R² = CH₃, X = Cl
2 = *R*-(-), R¹ = C₁₇H₃₃ **4** = 3-halo-*sn*, R¹ = C₁₇H₃₃, R² = C₁₅H₃₁, X = I
5 = 1-halo-*sn*, R¹ = C₁₇H₃₃, R² = C₁₅H₃₁, X = Cl
6 = 1-halo-*sn*, R¹ = C₁₇H₃₃, R² = C₁₇H₃₃, X = Br
7 = 1-halo-*sn*, R¹ = C₁₇H₃₃, R² = CH₃, X = I

i) Bu₄NX / (RCO)₂O / TMSX, CHCl₃, 80 °C / 30 min - 5 h

Scheme 1.



R¹, R² = alkyl or aryl; Q⁺ = Bu₄N⁺; X = Cl, Br or I

Scheme 2.

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