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# 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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**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 ($Bu_4NX$, 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.


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 $CrO_2Cl_2$,[21,22] $CoCl_2$,[23] $Bu_2SnCl_2/Ph_3P$,[24] or hexaalkylguanidinium chloride[25]) or parent haloacylating agents (e.g., $TiCl_4$/EtOAc/imidazole[26]) 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 $SnX_2$-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 alone[28] or as in a most recent variant of this method, in which a bromoacylating species was generated in situ from either LiBr-carboxylic acid anhydrides[4] 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: $Bu_4NBr$-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]

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Herein, we report that the same type of a reagent system, that is, CAA-TMSX-$Bu_4NX$ (X = Cl, Br or I), when applied to oxirane derivatives, effects a regiospecific 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 $Bu_4NX$ (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 $^{13}C$ 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 $^1H/^{13}C$ 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.

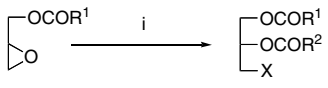
Since treatment of the carboxylic acid anhydrides at room temperature with TMSX (1.0 equiv) alone, or in the presence of 2.0–4.0 equiv of $Bu_4NX$ (e.g., X = Br, or I), led to almost instantaneous production of equimolar amounts of the corresponding acyl halides (AcX) and trimethylsilyl esters (AcTMS),[33] mechanistic contribution of these species to the haloacylating fission of the oxirane ring was examined next.

Model experiments (in $CHCl_3$/80 °C/1–6 h/pressure tube) supported by $^1H$ and $^{13}C$ 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 $Bu_4NBr$ (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 $Bu_4NBr$ (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 $Bu_4NI$ (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-



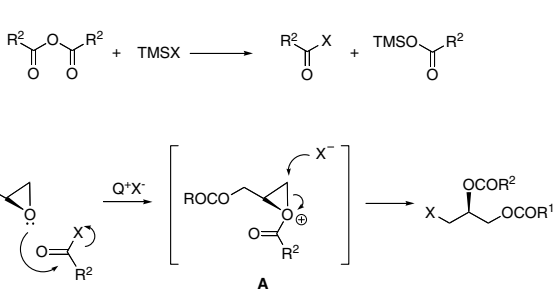

**1, 2** **3 - 7**

Isolated yields: 90 - 94%

**1** = *S-(+)*, $R^1 = C_{17}H_{33}$ **3** = 3-halo-*sn*, $R^1 = C_{17}H_{33}$, $R^2 = CH_3$, X = Cl
**2** = *R-(-)*, $R^1 = C_{17}H_{33}$ **4** = 3-halo-*sn*, $R^1 = C_{17}H_{33}$, $R^2 = C_{15}H_{31}$, X = I
**5** = 1-halo-*sn*, $R^1 = C_{17}H_{33}$, $R^2 = C_{15}H_{31}$, X = Cl
**6** = 1-halo-*sn*, $R^1 = C_{17}H_{33}$, $R^2 = C_{17}H_{33}$, X = Br
**7** = 1-halo-*sn*, $R^1 = C_{17}H_{33}$, $R^2 = CH_3$, X = I

i) $Bu_4NX$ / ('RCO)$_2$O / TMSX, $CHCl_3$, 80 °C / 30 min - 5 h

**Scheme 1.**




$R^1$, $R^2$ = alkyl or aryl; $Q^+ = Bu_4N^+$; X = Cl, Br or I

**Scheme 2.**

lides, the oxirane systems studied were completely inert toward $Bu_4NX$ (X = Cl, Br, or I) or AcTMS.

The formation in the investigated reactions of halohydrin derivatives **3**–**7** with defined stereochemistry and the lack of acyl migration (or generation of by-products with a carboxylate substituted halo-fragments within the glycerol unit) are in agreement with the above mechanism.

In conclusion, we have developed an efficient synthetic strategy for a direct haloacylating cleavage of glycidol esters to produce 2-*O*-acylated vicinal halohydrins using CAA-TMSX-$Bu_4NX$ (X = Cl, Br or I) reagent system. The main features of this new protocol are: (i) highly regioselective and stereospecific generation under mild conditions of 1,2(2,3)-diacyl-3(1)-halo-*sn*-glycerols as structurally defined three-carbon units with pre-designed asymmetry; (ii) the reactions are clean and allow chloro-, bromo-, or iodo-hydrin derivatives to be synthesized by means of the same procedure in high yields; (iii) the method seems to be general, makes use of commercially available reactants, and can easily be scaled up.

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34. General procedure for the synthesis of **3**–**7**. (*S*)-(+)-2-(Oleoyloxymethyl)oxirane **1** and (*R*)-(−)-2-(oleoyloxymethyl)oxirane **2** were obtained in one step via acylation of the corresponding chiral glycidols as described elsewhere.[30,31] To a solution of the starting substrate (**1** or **2**, 1.00 mmol) and tetra-*n*-butylammonium halide (2.00 mmol) in alcohol-free chloroform (3.0 mL), a mixture of the corresponding carboxylic acid anhydride (3.00 mmol) and trimethylsilyl halide (1.30 mmol), prepared in the same solvent (3.0 mL), was added and the reaction system was kept under argon in a pressure-proof glass ampoule at 80 °C (bath) for 30 min–5 h. The solution was passed through a chloroform-filled aluminum oxide pad (∼5 g) and the support was washed with the same solvent (∼150 mL). The volatile products were removed under reduced pressure and bis(acylated) haloglycerol **3**–**7** was isolated in pure state (purity >99%, $^1$H NMR spectroscopy) by flash column chromatography (silica gel; mobile phase for **3** and **7**, pentane–toluene–EtOAc 40:50:10, v/v/v; for **4**–**6**, toluene).
1-Oleoyl-2-acetyl-3-chloro-*sn*-glycerol **3**. Obtained from **1** (0.338 g, 1.00 mmol), $Bu_4NCl$ (0.556 g, 2.00 mmol), acetic anhydride (0.284 mL, 3.00 mmol), and TMSCl (0.164 mL, 1.30 mmol) for 3 h. Yield: 0.375 g (90%, colorless oil); $R_f$ = 0.62 (pentane–toluene–EtOAc, 40:50:10, v/v/v); $[\alpha]_D^{20}$ = +1.34 (*c* 6.37, $CHCl_3$); Anal. Calcd for $C_{23}H_{41}ClO_4$ (417.02): C, 66.24; H, 9.91; Cl, 8.50%. Found: C, 66.33; H, 9.89; Cl, 8.55%.
1-Oleoyl-2-palmitoyl-3-iodo-*sn*-glycerol **4**. Obtained from **1** (0.338 g, 1.00 mmol), $Bu_4NI$ (0.739 g, 2.00 mmol), palmitic anhydride (1.48 g, 3.00 mmol), and TMSI (0.177 mL, 1.30 mmol) for 1 h. Yield: 0.655 g (93%, colorless oil); $R_f$ = 0.80 (pentane–toluene–EtOAc, 40:50:10, v/v/v); $[\alpha]_D^{20}$ = +3.58 (*c* 11.40, $CHCl_3$); Anal. Calcd for $C_{37}H_{69}IO_4$ (704.85): C, 63.05; H, 9.87; I, 18.00%. Found: C, 63.01; H, 9.83; I, 18.07%.
1-Chloro-2-palmitoyl-3-oleoyl-*sn*-glycerol **5**. Obtained from **2** (0.338 g, 1.00 mmol), $Bu_4NCl$ (0.556 g, 2.00 mmol), palmitic anhydride (1.48 g, 3.00 mmol), and TMSCl (0.164 mL, 1.30 mmol) for 5 h. Yield: 0.552 g (90%, colorless oil); $R_f$ = 0.69 (pentane–toluene–EtOAc, 40:50:10, v/v/v); $[\alpha]_D^{20}$ = −2.10 (*c* 9.31, $CHCl_3$); Anal.

Calcd for $C_{37}H_{69}ClO_4$ (613.39): C, 72.45; H, 11.34; Cl, 5.78%. Found: C, 72.47; H, 11.32; Cl, 5.82%.

1-Bromo-2,3-dioleoyl-*sn*-glycerol **6**. Obtained from **2** (0.338 g, 1.00 mmol), $Bu_4NBr$ (0.645 g, 2.00 mmol), oleic anhydride (1.64 g, 3.00 mmol), and TMSBr (0.169 mL, 1.30 mmol) for 1.5 h. Yield: 0.643 g (94%, colorless oil); $R_f = 0.69$ (pentane–toluene–EtOAc, 40:50:10, v/v/v); $[\alpha]_D^{20} = -2.84$ (*c* 9.98, $CHCl_3$); lit.[2] 1,2-dioleoyl-3-bromo-*sn*-glycerol: $[\alpha]_D^{20} = +2.9$ (*c* 10, $CHCl_3$); Anal. Calcd for $C_{39}H_{71}BrO_4$ (683.88) requires C, 68.49; H, 10.46; Br, 11.68%. Found: C, 68.50; H, 10.40; Br, 11.40%.

1-Iodo-2-acetyl-3-oleoyl-*sn*-glycerol **7**. Obtained from **2** (0.338 g, 1.00 mmol), $Bu_4NI$ (0.739 g, 2.00 mmol), acetic anhydride (0.284 mL, 3.00 mmol), and TMSI (0.177 mL, 1.30 mmol) for 30 min. Yield: 0.478 g (94%, colorless oil); $R_f = 0.66$ (pentane–toluene–EtOAc, 40:50:10, v/v/v); $[\alpha]_D^{20} = -3.91$ (*c* 6.03, $CHCl_3$); Anal. Calcd for $C_{23}H_{41}IO_4$ (508.47): C, 54.33; H, 8.13; I, 24.96%. Found: C, 54.44; H, 8.10; I, 25.00%.