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Regioselective and Stereospecific Halosilylating Cleavage of the Oxirane System of Glycidol Derivatives as an Efficient Strategy to C2-*O*-Functionalized C3-Vicinal Halohydrins

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Glycidyl esters and ethers undergo a regioselective and stereospecific opening of the oxirane ring upon treatment with trimethylsilyl halides (TMSX, X = Cl, Br, or I) in the presence of pyridine to produce the corresponding C2-*O*-trimethylsilyl-3(1)-halo-*sn*-glycerols in high yields. Trifluoroacetylation across the trimethylsilyloxy system of such C3-synthons with trifluoroacetic anhydride (TFAA) in the presence of a halide anion (e.g. Bu_4NX; X = Cl, Br, or I), followed by removal of the trifluoroacetyl transient protection, provides nearly quantitative access to the respective vicinal haloalkanols. Alternatively, C2-*O*-acylated vicinal halohydrins can be obtained in a highly chemo-/regiospecific manner by direct conversion of the trimethylsilyl protecting group into short- or long-chain ester functionalities by means of a three-component reagent: pyridine–carboxylic acid–TFAA.

Introduction

Vicinal halohydrins (VHs) are among the most versatile synthetic intermediates that provide access to a vast array of functional groups[1] and biologically active compounds,[2] including lipid mediators,[3–7] halogenated marine natural products,[8] and others.[9] Halohydrins are substrates for a particular class of enzymes, halohydrin dehalogenases, and they are also of interest to both asymmetric synthesis[9] (e.g., chiral resolution of racemic synthons[10]) and bioremediation of the environment (e.g., the removal of pollutants from soil, groundwater or waste water[11]).

Because the addition of hypohalous acids and hypohalites to olefins[12] usually shows low regioselectivity and functionalization of glycerol staring materials,[4–7,13] requires multistep reaction sequences, and painstaking chromatographic separations of the target conjugates from the accompanying byproducts at each synthetic stage, the opening of oxirane systems with various nucleophiles seemed to be a much more attractive approach to VHs.[14] Nevertheless, regioselective and stereospecific incorporation of a halogen atom, even into a fairly simple three-carbon unit (e.g., glycerol), could still be an issue. For example, direct methods for converting oxiranes into halohydrins (e.g., by means of metal halides,[15,16] ammonium halides,[17] hydrohalides,[18] elemental halogens,[19] etc.) often suffer from low-to-moderate regioselectivity,[20] substrate incompatibility,[21] excessive expense,[22] poor availability[23,24] of the reagents employed, or afford mixture of stereoisomers.[15] One should mention that regioselectivity of the opening of an epoxide ring can be significantly increased if an additional functionality permitting coordination of metal cation[24] or boranes[25] is present.

An alternative two-step tactic involving insertion of organosilicon halides into epoxides[26] with a subsequent deprotection of the thus obtained *O*-silylated precursors of vicinal halohydrins[24] is incapable to circumvent the aforementioned shortcomings, as (i) halosilylating fission of oxiranes is not always completely regioselective and varies widely depending upon steric factors in the substrates[24,26] and (ii) the removal of relatively labile trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBDMS) ethers requires conditions that either preclude access to derivatives with acid-,[24] base-,[27] or oxidation/reduction-sensitive functionalities,[28] or they are known to trigger prohibitive structural rearrangements of the molecular skeleton (e.g., acyl migration, racemization, etc.) after exposure of a free hydroxy group adjacent to an acyl substituent.[27,29,30]

Despite the growing interest in vicinal haloesters (VHEs) as building blocks in the synthesis of structurally defined bioconjugates[3–7,31] of significance to membranology,[32] enzymology,[33] gene therapy,[13] and drug design,[34] oxirane chemistry has not been exploited to any significant extent to produce such a type of *O*-functionalized VH. This is probably due to the fact that existing protocols based on electrophilic cleavage of terminal epoxides with acyl chlo-

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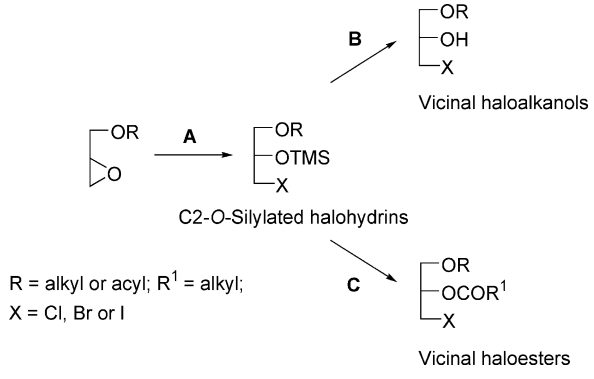
rides (e.g., alone[35] or in combination with CrO_2Cl_2,[36] $CoCl_2$,[37] Bu_2SnCl_2/Ph_3P,[38] or hexaalkylguanidinium chloride[39]) or related haloacylating systems (e.g., $TiCl_4$/EtOAc/imidazole[40]), are usually limited by competing side reactions or incompatibility with oxidation/Lewis acid sensitive substrates, and only low-reactive *O*-acylated vicinal chlorohydrins are afforded.[5]

The use of acyl bromides,[41] or a parent species generated in situ from either LiBr–carboxylic acid anhydrides[42] or LiBr–oleic anhydride–benzyltributylammonium bromide[43] for haloacylation of glycidyl esters does not provide remedy for these problems either, as the approaches appeared to be restricted to the production of bromo derivatives, or the reaction conditions do not secure complete stereochemical homogeneity of the preparations.[43]

In this context, opening of an epoxide ring to form an *O*-silylated halohydrin intermediate, followed by direct esterification across the *O*-silyl group without exposing a free hydroxy functionality seemed a viable route to VHEs. Unfortunately, the sole literature precedent reports a SnX_2-promoted fission of 2,3-epoxy ethers with trimethylsilyl halides (TMSX, X = Cl or Br), which, after acylation, gives rise to only 2-acetyl-3-halohydrins in rather erratic yields and with mediocre regioselectivity.[44] Attempted extension of this methodology to the synthesis of chloroester derivatives from the respective glycidyl esters resulted in extensive (~80%) acyl migration.[44]

To address the above problems, in this paper we describe a simple and efficient protocol for the synthesis of configurationally pure C3-chloro-, bromo-, and iodohydrins bearing a vicinal *O*-trimethylsilyl substituent (route A), a hydroxy group (route B), or acyl functionalities (route C) obtainable in high yields and under mild conditions from a single glycidyl precursor (Scheme 1). A preliminary account of part of this work has recently been communicated.[45]



Scheme 1.

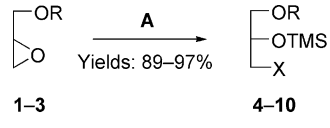
Results and Discussion

In the following sections, we will discuss the reaction pathways and possible mechanisms regarding the regioselective and stereospecific (i) halosilylating ring cleavage of glycidyl esters and ethers with trimethylsilyl halides (TMSX, X = Cl, Br, or I) in the presence of pyridine to give C2-*O*-trimethylsilylated haloglycerols (route A, Scheme 2) as common precursors to either vicinal haloalkanols or their haloesters, (ii) transformation of the produced trimethylsilyl derivatives into the corresponding C3-vicinal haloalkanols with the intermediacy of *O*-trifluoroacetates (route B, Scheme 4), and (iii) production of C2-*O*-acylated C3-vicinal halohydrins by direct replacement of the trimethylsilyl group with a short-/long-chain fatty acid residue effected by a three-component reagent system, pyridine–carboxylic acid (CA)–trifluoroacetic acid (TFAA) (route C, Scheme 6).

Because the depicted transformations apparently occur without exposure of a free hydroxy functionality within the glycerol skeleton, they may constitute a novel strategy for the synthesis of structurally defined C2-*O*-functionalized C3-vicinal halohydrins and related compounds, which should eliminate a perennial problem of glycerolipid chemistry, namely, acyl migration.[29,46]

Synthesis of C2-*O*-Trimethylsilylated C3-Vicinal Halohydrins (4–10) (Route A, Scheme 2)

For the initial experiments, as a representative substrate, a racemic glycidyl oleate (racemic **1**, Scheme 2) having an acyl group prone to migration, was chosen. Attempted opening of the oxirane system by treatment of glycidyl oleate (**1**) in aprotic solvents (e.g., CH_2Cl_2 or $CHCl_3$) with acetyl bromide (3.0 equiv.) at room temperature for 12–24 h produced complex reaction mixtures consisting of the starting material (~30%), 1,3-dibromo-2-oleoylglycerol (~20%), and 1-oleoyl-2-acetyl-3-bromoglycerol (~35%) and its isomeric 1-acetyl-2-oleoyl derivative (~15%) (TLC, ^1H and ^{13}C NMR spectroscopic analyses). Replacement of acetyl bromide by trimethylsilyl bromide (TMSBr, 3.0 equiv.) under the same conditions led to practically quantitative formation of undesired 1,3-dibromo-2-oleoylglycerol (isolated in 91% yield).

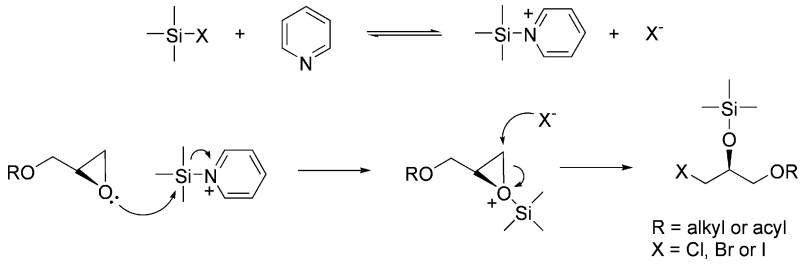


1 = *S*-(+), R = $C_{17}H_{33}CO$ **4** = 3-halo-*sn*, R = $C_{17}H_{33}CO$, X = Cl
2 = *R*-(–), R = $C_{17}H_{33}CO$ **5** = 1-halo-*sn*, R = $C_{17}H_{33}CO$, X = Cl
3 = *rac*, R = $C_{16}H_{33}$ **6** = 3-halo-*sn*, R = $C_{17}H_{33}CO$, X = Br
7 = 1-halo-*sn*, R = $C_{17}H_{33}CO$, X = Br
8 = 3-halo-*sn*, R = $C_{17}H_{33}CO$, X = I
9 = 1-halo-*sn*, R = $C_{17}H_{33}CO$, X = I
10 = *rac*, R = $C_{16}H_{33}$, X = Cl

Route A: TMSX (1.5 equiv.), pyridine (6.0 equiv.), $CHCl_3$
r.t., ca. 6 min (for iodohydrins) or
80 °C, 30 min/7 h (for bromo-/chlorohydrins, respectively)

Scheme 2.

Analysis of the chemical structures of the byproducts indicated that the initially formed bromohydrin intermediates probably underwent a competing acyl migration (triggered, most likely, by intramolecular addition to the adjacent carbonyl functionality to form a tetrahedral inter-



Scheme 3.

mediate), which led to compounds with the oleoyl group at the C2 position. To remedy this problem, we tried to carry out the reactions in the presence of pyridine to increase trapping efficiency of the incipient hydroxy functional group in the form of acetate. Indeed, the course of the reaction was dramatically changed when the oxirane ring opening was carried out in the presence of a small amount of pyridine. In this instance, treatment of glycidyl oleate (**1**) with acetyl bromide (3.0 equiv.) in chloroform containing pyridine (6.0 equiv.) at 80 °C (pressure tube) for 0.5–3 h resulted in highly regioselective formation of the expected 1-oleoyl-2-acetyl isoster (isolated in >90% yields; purity >99% as judged by ^{1}H and ^{13}C NMR spectroscopy).

Although these preliminary results were most encouraging, the poor availability of acyl halides derived from long-chain fatty acids (especially the corresponding bromides and iodides), would make the scope of this reaction rather narrow. Besides, the approach cannot be applied if C3-vicinal haloalkanols incorporating a terminal acyl substituent are desired. Therefore, we turned our attention to trimethylsilyl halides (TMSX, X = Cl, Br, or I) as an alternative to acyl halide agents for fission of oxiranes. These, in combination with pyridine, were expected to provide convenient entry to 2-*O*-silylated halohydrins as prospective synthons in the synthesis of vicinal haloalkanols and vicinal haloesters.

Indeed, the reaction of TMSBr (3 equiv.) with oleate **1** in chloroform in the presence of pyridine produced cleanly 1-oleoyl-2-*O*-trimethylsilyl-3-bromoglycerol (racemic **6** in Scheme 2). After evaluation of various reaction conditions, the best results were obtained when a solution of glycidyl derivatives **1**–**3** and pyridine (6.0 equiv.) in chloroform was treated with TMSX (1.5 equiv.) as shown in Scheme 2. For trimethylsilyl iodide, the halosilylation went to completion within a few minutes at room temperature, whereas for the other halide derivatives, the reaction times were longer and required thermal treatment in a pressure flask at 80 °C (30 min for bromides, and ca. 7 h for chlorides). The ^{1}H and ^{13}C NMR spectra of the isolated products revealed that in all instances the conversion to target silyl ethers **4**–**10** was nearly quantitative and entirely chemo- and regioselective (>99%). The reaction seemed to be rather general, as other glycidol conjugates (e.g., benzoyl, linoleoyl, isopropyl, or *tert*-butyldiphenylsilyl; results not shown) also underwent nearly quantitative transformation into the corresponding 2-*O*-trimethylsilylated vicinal halohydrins.

The exclusive formation of 2-*O*-silyl derivatives **4**–**10** with defined stereochemistry (e.g., **4**–**9**) suggested that the oxirane ring opening in **1**–**3** with TMSX occurred by nucleophilic attack of the halide anion at the primary carbon center with simultaneous formation of the silyl ether bond, as shown in Scheme 3. The absence of bis(halogenated) by-products indicated a critical role of pyridine in this reaction, which can be due both to releasing a halide nucleophile from TMSX and generation of a highly electrophilic species, the *N*-silylpyridinium cation. Because the latter is expected to act as a powerful electrophilic catalyst, the opening of the oxirane ring and silylation of the incipient 2-hydroxy functionality are likely to be a synchronous process, which should occur without scrambling of the adjacent acyl moiety.

Synthesis of C3-Vicinal Haloalkanols (16–20) (Route B, Scheme 4)

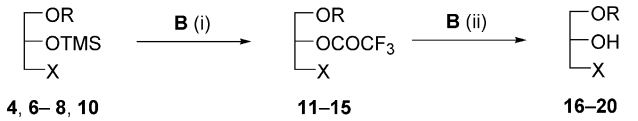
Having developed the reaction conditions for the production of 2-*O*-trimethylsilylated haloglycerols from the corresponding glycidyl derivatives **1**–**3**, we were interested in a direct transformation of **4**–**10** into the respective trifluoroacetyl esters to alleviate drawbacks inherent to direct deprotection of the silyl precursors.[47]

The important point of introducing a trifluoroacetyl functionality into a molecule is that it confers stability to the framework organization (e.g., prevents scrambling of acyl residues within the glycerol skeleton) and on this basis a convenient storage form for labile, biologically active glycerolipids has been proposed.[48] The added value of the trifluoroacetyl protection is that this group can be removed quantitatively under mild conditions to provide pure target compounds without any additional workup or chromatographic purification.[48,49]

Examples of a direct conversion of various silyloxy systems (e.g., trimethylsilyl-, *tert*-butyldimethylsilyl-, triisopropylsilyl-, *tert*-butyldiphenylsilyl ethers, etc.) into either acetates (e.g., by using $FeCl_3$–acetic anhydride,[50] pyridine–acetic anhydride–acetic acid, methanol–acetic acid,[51] $ZnCl_2$–acetyl chloride,[52] or $SnBr_2$–acetyl bromide[53]) or higher carboxylates[54] are known from the literature. These methods, however, (i) involve chemical procedures that are incompatible with trifluoroacetyl derivatives, (ii) are not selective towards any of the commonly employed silyl transient protections, and (iii) are inapplicable to the synthesis of C3-vicinal haloalkanols bearing a terminal acyl group.

To remedy these problems, the reaction conditions for direct trifluoroacetylation of 2-*O*-trimethylsilylated halogly-

cerides having representative acyl- (compounds **4**, **6**–**8**) or alkyl groups (compound **10**) with TFAA in the presence of a halide ion were investigated by changing the type of solvent, ratio of the reactants, etc. [route B (i), Scheme 4].



4, **11, 16** = 3-halo-*sn*, R = $C_{17}H_{33}CO$, X = Cl
6, **12**, **17** = 3-halo-*sn*, R = $C_{17}H_{33}CO$, X = Br
7, **13**, **18** = 1-halo-*sn*, R = $C_{17}H_{33}CO$, X = Br
8, **14**, **19** = 3-halo-*sn*, R = $C_{17}H_{33}CO$, X = I
10, **15**, **20** = *rac*, R = $C_{16}H_{33}$, X = Cl

Route B: (i) $(F_3CCO)_2O$ (2.0 equiv.), Bu_4NX (2.0 equiv.), $CHCl_3$, r.t., 5 h; (ii) pyridine (10 equiv.), MeOH (250 equiv.), CH_2Cl_2/pentane, r.t., 20 min.

Scheme 4.

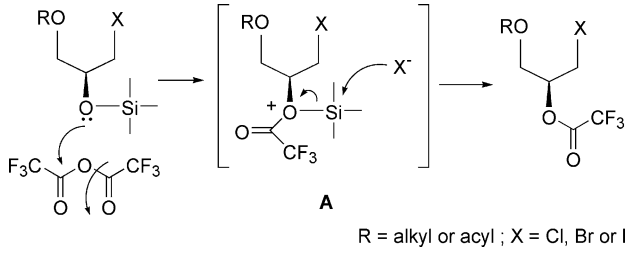
It was found that when TFAA (2.0 equiv.) was added to **4**, **6**–**8**, **10**, and Bu_4NX (2.0 equiv., X = Cl, Br, or I) in chloroform, and the reaction mixture was left at room temperature for 4–5 h, trifluoroacetates **11**–**15** were formed quantitatively and in a highly chemo- and regiospecific fashion (>99%, ^1H and ^{13}C NMR spectroscopy). Compounds **11**–**15** were isolated in 91–95% yield after simple solid-phase filtration through a short silica gel pad (see Experimental Section). To avoid side-product formation due to a possible halogen-exchange process, the halide anion used was matched to that present in halohydrins **4**, **6**–**8**, and **10**.

The kinetics of the above transformations was not appreciably affected by electronic features or the type of the functional groups present in **4**, **6**–**8**, and **10** (e.g., acyl vs. alkyl group or chloride vs. bromide or iodide) or the kind of the halide ion used. Other trimethylsilyl-protected primary, secondary, or sterically hindered alcohols (e.g., 1,3-propanediol, cholesterol, α-tocopherol, etc.) also underwent quantitative trifluoroacetylation, with a notable exception of triisopropylsilyl- and *tert*-butyldiphenylsilyl ethers, which turned out to be completely stable under the reaction conditions.

Mechanistic studies supported by ^1H and ^{13}C NMR spectroscopy (Table 1) showed that TFAA alone (entry 1) effected trifluoroacetylation across the trimethylsilyloxy system of compound **8** to produce trifluoroacetate **14**, but the reaction was sluggish and did not go to completion at room temperature for 1 week.

Other carboxylic acid anhydrides (e.g. acetic anhydride), when used either alone or in combination with Bu_4NX (X = Cl, Br, or I), remained essentially unreactive even at elevated temperatures (entry 2). As shown in entry 3, TFAA in the presence of TMSX (X = Cl, Br, or I), was also inefficient in replacing the trimethylsilyl group in the model substrate by a trifluoroacetyl one, although it is known that this system generates highly electrophilic species, trifluoroacetyl halides.[54] The latter reactions, however, could be rescued by the addition of the corresponding Bu_4NX (entry 4).

The above observations are consistent with a mechanism (Scheme 5) that involves initial coordination of a trifluoroacetyl group to the oxygen atom of the silyloxy system, followed by nucleophilic attack of a halide ion on the silicon center in intermediate **A** to produce the ester bond. The combination of nucleophile and electrophile catalysis rationalizes the fact that under the reaction conditions the replacement of the TMS protection by the trifluoroacetyl group occurs without scrambling of the proximate acyl



Scheme 5.

Table 1. Mechanistic studies.

No	Reaction conditions (in $CHCl_3$)[a]	Temp.	Time
1	OCOR, OTMS, I — TFAA (3.0 equiv.), yield: ca. 70% → OCOR, $OCOCF_3$, I	r.t.	7 d
2	OCOR, OTMS, I — Ac_2O (2.0 equiv.)/Bu_4NI (2.0 equiv.) → No reaction	80 °C	1 h
3	OCOR, OTMS, Br — TFAA (4.0 equiv.)/TMSBr (2.0 equiv.) → No reaction	r.t.	8 h
4	OCOR, OTMS, Br — TFAA (4.0 equiv.)/TMSBr (2.0 equiv.)/Bu_4NBr (2.0 equiv.), yield: ca.95% → OCOR, $OCOCF_3$, Br	r.t.	4 h

[a] RCO = oleoyl; Bu_4N = tetra-*n*-butylammonium; TFAA = $(CF_3CO)_2O$; TMS = trimethylsilyl.

moiety (if present), as no free hydroxy group of the glycerol skeleton is exposed. In addition, as no C–O bond scission takes place at the stereogenic carbon center, the transformation should be stereospecific and occur with retention of configuration. Fair independence of the rate of trifluoroacetylation on the nature of the external halide used, as well as the formation of only 2-*O*-trifluoroacetylated halohydrins **11**–**15** [route B (i), Scheme 4] with defined stereochemistry (see Experimental Section), and the lack of an intramolecular acyl rearrangement, are in agreement with this mechanism.

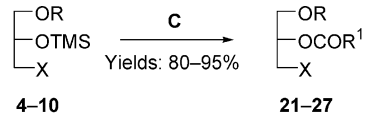
An alternative scenario that would invoke nucleophilic attack by a trifluoroacetate anion on silicon seems less plausible, as halide ions are apparently more effective as a nucleophile for silicon than trifluoroacetate. This is also in line with the experimental data that trifluoroacetylation was significantly faster in the presence of external halides.

The obtained trifluoroacetyl derivatives (e.g., **11**–**15**) can either be stored for several weeks (–20 °C, under an atmosphere of argon) without detectable alterations of their spectral characteristics (^{1}H and ^{13}C NMR spectroscopy) or to be employed directly as starting materials for the synthesis of vicinal halohydrins.

To this end, intermediary trifluoroacetates **11**–**15** were treated in CH_2Cl_2/pentane with pyridine (10 equiv.) and methanol (250 equiv.) at room temperature. The reactions were quantitative (completion within 20 min) and after removal of volatile products, afforded positionally homogeneous vicinal haloalkanols **16**–**20** (purity >99%, ^{1}H and ^{13}C NMR spectroscopy) without any supplementary purification [route B (ii), Scheme 4].

Synthesis of C3-Vicinal Haloesters (21–27) (Route C, Scheme 6)

As part of our program on new synthetic approaches to glycerolipids,[48,49,55] we developed recently a three-component system, namely Bu_4NBr–TMSBr–carboxylic acid anhydrides, that efficiently effected replacement of silyl transient protections by short- or long-chain acyl residues directly.[54] Although utility of this reagent can be extended to the production of vicinal bromoesters, it appeared to be less suitable for the synthesis of C2-*O*-acylated C3-vicinal chloro- and iodohydrins from the corresponding *O*-trimethylsilyl congeners (e.g., type **4** and **8**, Scheme 6) as a result of the competitive formation of bromohydrin byproducts (ca. 10-20%, ^{1}H and ^{13}C NMR spectroscopy). To alleviate this problem, we focused on mixed carboxylic anhydrides that have recently been advocated as reagents for acylolytic cleavage of some acetals.[56]



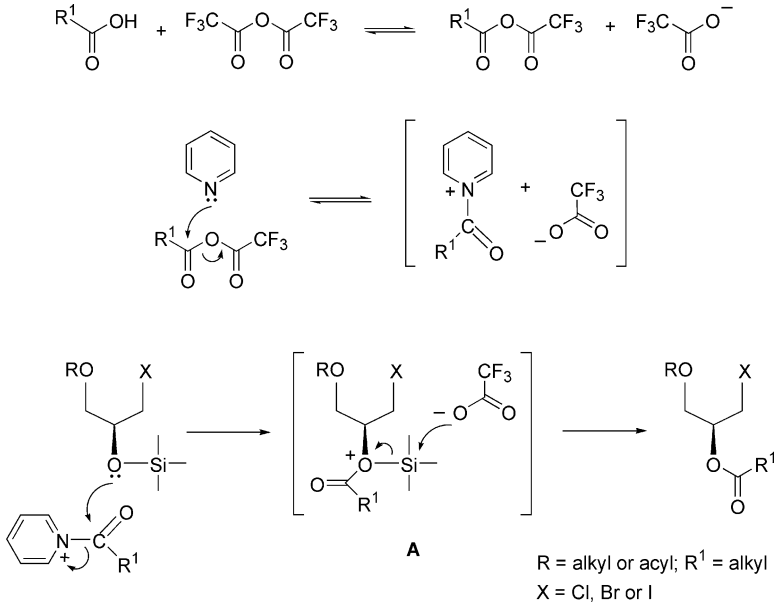
4–**10** **21**–**27**

4, **21** = 3-halo-*sn*, R = $C_{17}H_{33}CO$, ^{1}R = CH_3, X = Cl
5, **22** = 1-halo-*sn*, R = $C_{17}H_{33}CO$, ^{1}R = $C_{15}H_{31}$, X = Cl
6, **23** = 3-halo-*sn*, R = $C_{17}H_{33}CO$, ^{1}R = $C_{17}H_{33}$, X = Br
7, **24** = 1-halo-*sn*, R = $C_{17}H_{33}CO$, ^{1}R = $C_{17}H_{33}$, X = Br
8, **25** = 3-halo-*sn*, R = $C_{17}H_{33}CO$, ^{1}R = CH_3, X = I
9, **26** = 1-halo-*sn*, R = $C_{17}H_{33}CO$, ^{1}R = $C_{15}H_{31}$, X = I
10, **27** = *rac*, R = $C_{16}H_{33}$, ^{1}R = CH_3, X = Cl

Route C: pyridine (6.0 equiv.), CH_3COOH, $C_{15}H_{31}COOH$ or $C_{17}H_{33}COOH$ (6.0 equiv.), TFAA (1.5 equiv.), $CHCl_3$, 80 °C, 3–7 h.

Scheme 6.

After evaluating various experimental conditions,[45] in optimized runs a solution of silyl ethers **4**–**10** and pyridine (6.0 equiv.) in chloroform was treated in a pressure ampoule at 80 °C for 3–7 h with a mixture of the appropriate carboxylic acid (6.0 equiv., acetic, palmitic or oleic acid) and trifluoroacetic anhydride (TFAA, 1.5 equiv.) (Scheme 6). ^{1}H



Scheme 7.

and ^{13}C NMR spectra of the isolated compounds showed that the conversion of **4**–**10** into target haloesters **21**–**27** was consistently high yielding (80-95%) and occurred in a strictly chemo- and regioselective manner (>99%). For these reactions, no significant differences in rates were observed for the substrates examined.

TFAA seemed to be an indispensable component of the reagent system, as other carboxylic acid anhydrides (including acetic anhydride) were completely unreactive (even in neat pyridine), in an attempted replacement of the trimethylsilyl group in compounds **4**–**10**. It should be mentioned that sterically hindered silyl ethers (e.g., *tert*-butyldimethylsilyl-, triisopropylsilyl-, or *tert*-butyldiphenylsilyl derivatives of oleyl alcohol, cholesterol, etc.) were also stable under the reaction conditions when TFAA was used.

Consistent with the above facts, a tentative mechanism for the displacement of a trimethylsilyl group by an acyl moiety by using a three-component reagent system (i.e. CA–TFAA–pyridine) is shown in Scheme 7. It involves generation of the mixed carboxylic–trifluoroacetic anhydride from the corresponding carboxylic acid and TFAA (probably mediated by pyridine), followed by its activation by pyridine, which results in the formation of reactive *N*-acylpyridinium cation. The latter species is expected to be a strong electrophile that may coordinate to the oxygen atom of the silicon center in **A**, which thus facilitates cleavage of the silicon–oxygen bond by the relatively weak nucleophile trifluoroacetate anion.

Conclusions

We developed a novel, simple, and efficient strategy for the synthesis of C2-*O*-functionalized C3-vicinal halohydrins. The protocol is based on a regioselective and stereospecific opening of the oxirane system of glycidyl esters and ethers with trimethylsilyl halides in the presence of pyridine to produce the corresponding 2-*O*-trimethylsilyl intermediate, followed by the replacement of the silyl group either by a trifluoroacetyl transient protection (using TFAA/Bu_4NX, X = Cl, Br, or I) or short-/long-chain acyl moiety (using CA–TFAA–pyridine), without exposing a free hydroxy functionality. The reactions are clean and allow chloro-, bromo-, or iodohydrin derivatives incorporating a vicinal silyl-, hydroxyl-, or ester functionality to be obtained from a single glycidol precursor under mild conditions and in high yields. The approach seems to be general, makes use of commercially available reactants, and can easily be scaled up.

Experimental Section

General: All reagents were commercial grade (Fluka, Lancaster, Merck, Sigma) with purity >98% and were used as provided. Solvents were dried and distilled prior to use according to standard protocols.[57] Reaction conditions were kept strictly anhydrous unless otherwise stated. Progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on precoated glass plates of silica gel 60 F_{254} (Merck). The spots were visualized by using the commercially available 3.5% molybdatophosphoric acid spray reagent (Merck) or 50% sulfuric acid followed by heating at 140 °C. Column chromatography (CC) was carried out on silica gel 60 (70-230 mesh ASTM, Merck) by using appropriate solvent systems (see below). ^1H and ^{13}C NMR spectra were recorded with a Varian 400 MHz machine and chemical shifts are reported in ppm relative to TMS. The assignment of proton and carbon resonances of **1**–**27** was done on the basis of established or expected chemical shifts in conjunction with ^1H–^1H, ^1H–^{13}C, and DEPT correlated NMR spectroscopy. In several instances, ^1H and ^{13}C NMR spectral characteristics of known compounds were also included to make up for a deficiency of relevant literature information. Optical rotations were measured with a Perkin–Elmer 241 digital polarimeter. Melting points were determined with a Kofler melting point apparatus and are uncorrected. (*S*)-(+)-2-(Oleoyloxymethyl)oxirane (**1**) [colorless oil. $[\alpha]_D^{20}$ = +13.79 (*c* = 5.18, $CHCl_3$)] and (*R*)-(–)-2-(oleoyloxymethyl)oxirane (**2**) [colorless oil. $[\alpha]_D^{20}$ = –13.60 (*c* = 6.11, $CHCl_3$)] were prepared by acylation of chiral glycidols with oleoyl chloride (all from Fluka) as described elsewhere.[49] (*rac*)-(±)-2-(Hexadecyloxymethyl)oxirane (**3**) (white solid, m.p. 34.0-35.1 °C) was obtained from racemic glycidyl tosylate (Fluka) in two steps by following a standard approach.[58] No attempts were made to optimize these particular procedures that provided glycidyl substrates **1**–**3** with spectral and physicochemical characteristics comparable to those reported in the literature.[49,58]

General Procedure for the Synthesis of C2-*O*-Trimethylsilylated C3-Vicinal Halohydrins 4–10 (Route A): To a solution of glycidyl substrate **1**–**3** (1.00 mmol) and pyridine (0.484 mL, 6.00 mmol) in alcohol-free chloroform (5.0 mL) was added a trimethylsilyl halide (1.50 mmol), and the reaction system was kept under an argon atmosphere either at room temperature for ca. 6 min or in a pressure-proof glass ampoule at 80 °C (bath) for 0.5–7 h. Solvents were removed under reduced pressure. *O*-Silylated halohydrins **4**–**10** were isolated in pure state (purity >99%, ^1H NMR spectroscopy) by flash column chromatography (silica gel, toluene).

1-Oleoyl-2-*O*-trimethylsilyl-3-chloro-*sn*-glycerol (4): Obtained from **1** (0.338 g, 1.00 mmol) and TMSCl (0.189 mL, 1.50 mmol) at 80 °C after 7 h. Yield: 0.411 g (92%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.77. $[\alpha]_D^{20}$ = +1.69 (*c* = 10.70, $CHCl_3$). $C_{24}H_{47}ClO_3Si$ (447.17): calcd. C 64.46, H 10.59, Cl 7.93; found C 64.53, H 10.53, Cl 7.90.

1-Chloro-2-*O*-trimethylsilyl-3-oleoyl-*sn*-glycerol (5): Obtained from **2** (0.338 g, 1.00 mmol) and TMSCl (0.189 mL, 1.50 mmol) at 80 °C after 7 h. Yield: 0.398 g (89%, colorless oil). $[\alpha]_D^{20}$ = –1.70 (*c* = 12.94, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **4**.

1-Oleoyl-2-*O*-trimethylsilyl-3-bromo-*sn*-glycerol (6): Obtained from **1** (0.338 g, 1.00 mmol) and TMSBr (0.195 mL, 1.50 mmol) at 80 °C after 30 min. Yield: 0.471 g (96%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.73. $[\alpha]_D^{20}$ = +1.91 (*c* = 13.10, $CHCl_3$). $C_{24}H_{47}BrO_3Si$ (491.62): calcd. C 58.63, H 9.64, Br 16.25; found C 58.72, H 9.59, Br 16.20.

1-Bromo-2-*O*-trimethylsilyl-3-oleoyl-*sn*-glycerol (7): Obtained from **2** (0.338 g, 1.00 mmol) and TMSBr (0.195 mL, 1.50 mmol) at 80 °C after 30 min. Yield: 0.474 g (96%, colorless oil). $[\alpha]_D^{20}$ = –1.88 (*c* = 10.11, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **6**.

1-Oleoyl-2-*O*-trimethylsilyl-3-iodo-*sn*-glycerol (8): Obtained from **1** (0.338 g, 1.00 mmol) and TMSI (0.204 mL, 1.50 mmol) at room temperature after ca. 6 min. Yield: 0.521 g (97%, colorless oil). R_f

(pentane/toluene/EtOAc, 40:50:10) = 0.76. $[\alpha]_D^{20}$ = +2.41 (*c* = 13.60, $CHCl_3$). $C_{24}H_{47}IO_3Si$ (538.62): calcd. C 53.52, H 8.79, I 23.56; found C 53.47, H 8.83, I 23.63.

1-Iodo-2-*O*-trimethylsilyl-3-oleoyl-*sn*-glycerol (9). Obtained from **2** (0.338 g, 1.00 mmol) and TMSI (0.204 mL, 1.50 mmol) at room temperature after ca. 6 min. Yield: 0.517 g (96%, colorless oil). $[\alpha]_D^{20}$ = –2.45 (*c* = 11.20, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **8**.

1-*O*-Hexadecyl-2-*O*-trimethylsilyl-3-chloro-*rac*-glycerol (10). Obtained from **3** (0.298 g, 1.00 mmol) and TMSCl (0.189 mL, 1.50 mmol) at 80 °C after 7 h. Yield: 0.362 g (89%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.81. $C_{22}H_{47}ClO_2Si$ (407.15): calcd. C 64.90, H 11.63, Cl 8.71; found C 64.95, H 11.59, Cl 8.68.

General Procedure for the Direct Transformation of C2-*O*-Trimethylsilyl Ethers 4, 6–8, and 10 Into *O*-Trifluoroacetates 11–15 [Route B (i)]: To a solution of silyl ether **4**, **6**–**8**, or **10** (1.00 mmol) and tetra-*n*-butylammonium halide (2.00 mmol) in alcohol-free chloroform (5.0 mL) was added trifluoroacetic anhydride (0.278 mL, 2.00 mmol), and the reaction was left under an argon atmosphere at room temperature for 5 h. Solvents were evaporated in vacuo, and the residue was taken into toluene (5.0 mL) and passed through a silica gel pad (~5 g) prepared in the same solvent. The support was washed with toluene (~100 mL), fractions containing the target compounds were combined, the eluent was removed under reduced pressure, and the residue was kept under high vacuum at room temperature for 2–3 h to give trifluoroacetate **11**–**15** (purity >99%, ^{1}H NMR spectroscopy).

1-Oleoyl-2-trifluoroacetyl-3-chloro-*sn*-glycerol (11): Obtained from **4** (0.447 g, 1.00 mmol) and Bu_4NCl (0.556 g, 2.00 mmol). Yield: 0.429 g (91%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.66. $[\alpha]_D^{20}$ = +0.28 (*c* = 9.65, $CHCl_3$). $C_{23}H_{38}ClF_3O_4$ (470.99): calcd. C 58.65, H 8.13, Cl 7.53; found C 58.70, H 8.09, Cl 7.55.

1-Oleoyl-2-trifluoroacetyl-3-bromo-*sn*-glycerol (12): Obtained from **6** (0.492 g, 1.00 mmol) and Bu_4NBr (0.645 g, 2.00 mmol). Yield: 0.490 g (95%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.69. $[\alpha]_D^{20}$ = +3.47 (*c* = 8.05, $CHCl_3$). $C_{23}H_{38}BrF_3O_4$ (515.44): calcd. C 53.59, H 7.43, Br 15.50; found C 53.63, H 7.40, Br 15.55.

1-Bromo-2-trifluoroacetyl-3-oleoyl-*sn*-glycerol (13): Obtained from **7** (0.492 g, 1.00 mmol) and Bu_4NBr (0.645 g, 2.00 mmol). Yield: 0.492 g (95%, colorless oil). $[\alpha]_D^{20}$ = –3.40 (*c* = 10.08, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **12**.

1-Oleoyl-2-trifluoroacetyl-3-iodo-*sn*-glycerol (14): Obtained from **8** (0.539 g, 1.00 mmol) and Bu_4NI (0.739 g, 2.00 mmol). Yield: 0.529 g (94%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.74. $[\alpha]_D^{20}$ = +6.40 (*c* = 10.01, $CHCl_3$). $C_{23}H_{38}F_3IO_4$ (562.44): calcd. C 49.11, H 6.81, I 22.56; found C 49.15, H 6.78, I 22.60.

1-*O*-Hexadecyl-2-trifluoroacetyl-3-chloro-*rac*-glycerol (15). Obtained from **10** (0.407 g, 1.00 mmol) and Bu_4NCl (0.556 g, 2.00 mmol). Yield: 0.396 g (92%, colorless oil). R_f = 0.82 (pentane/toluene/EtOAc, 40:50:10). $C_{21}H_{38}ClF_3O_3$ (430.97): calcd. C 58.52, H 8.89, Cl 8.23; found C 58.55, H 8.83, Cl 8.26.

General Procedure for the Cleavage of *O*-Trifluoroacetates 11–15 To Produce Vicinal Haloalkanols 16–20 [Route B (ii)]: To a solution of trifluoroacetylated halohydrin **11**–**15** (1.00 mmol) in pentane/CH_2Cl_2 (3:1, 5.0 mL), was added a mixture of pyridine (0.8 mL, 10 mmol) and methanol (10.1 mL, 250 mmol) in the same solvents (5.0 mL) at 0 °C, and the reaction mixture was left at room temperature for 20 min. Solvents were evaporated under reduced pressure (bath temp. 50 °C), and the residue was kept under high vacuum at room temperature for 2–3 h to give deprotected haloalkanols **16**–**20** (purity >99%, ^{1}H NMR spectroscopy).

1-Oleoyl-3-chloro-*sn*-glycerol (16): Obtained from **11** (0.471 g, 1.00 mmol). Yield: 0.375 g (100%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.31. $[\alpha]_D^{20}$ = +3.00 (*c* = 5.66, $CHCl_3$). $C_{21}H_{39}ClO_3$ (374.98): calcd. C 67.26, H 10.48, Cl 9.45; found C 67.30, H 10.52, Cl 9.40.

1-Oleoyl-3-bromo-*sn*-glycerol (17): Obtained from **12** (0.515 g, 1.00 mmol). Yield: 0.418 g (100%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.33. $[\alpha]_D^{20}$ = +2.45 (*c* = 8.53, $CHCl_3$). $C_{21}H_{39}BrO_3$ (419.44): calcd. C 60.13, H 9.37, Br, 19.05; found C 60.20, H 9.33, Br 19.00.

1-Bromo-3-oleoyl-*sn*-glycerol (18): Obtained from **13** (0.515 g, 1.00 mmol). Yield: 0.416 g (100%, colorless oil). $[\alpha]_D^{20}$ = –2.48 (*c* = 7.27, $CHCl_3$). All other physicochemical and spectral characteristics were identical with those of **17**.

1-Oleoyl-3-iodo-*sn*-glycerol (19): Obtained from **14** (0.562 g, 1.00 mmol). Yield: 0.466 g (100%, white solid, m.p. 33.0–33.6 °C). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.36. $[\alpha]_D^{20}$ = +2.39 (*c* = 8.37, $CHCl_3$); ref.[7] $[\alpha]_D^{20}$ = +1.9 (*c* = 10, $CHCl_3$) M.p. 33.4 °C. $C_{21}H_{39}IO_3$ (466.44): calcd. C 54.07, H 8.43, I 27.21; found C 54.14, H 8.40, I 27.26.

1-*O*-Hexadecyl-3-chloro-*rac*-glycerol (20): Obtained from **15** (0.431 g, 1.00 mmol). Yield: 0.334 g (100%, amorphous white solid). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.40. $C_{19}H_{39}ClO_2$ (334.96): calcd. C 68.13, H 11.74, Cl 10.58; found C 68.17, H 11.71, Cl 10.62.

General Procedure for the Direct Conversion of C2-*O*-Trimethylsilylated C3-Vicinal Halohydrins 4–10 Into Their C2-*O*-Acylated Isosteric Forms 21–27 (Route C): To a solution of the silylated halohydrins **4**–**10** (1.00 mmol) and pyridine (0.484 mL, 6.00 mmol) in alcohol-free chloroform (3.0 mL) was added a mixture of the requisite carboxylic acid (6.00 mmol) and trifluoroacetic anhydride (0.209 mL, 1.50 mmol), prepared in the same solvent (3.0 mL), and the reaction system was kept under an atmosphere of argon in a pressure-proof glass ampoule at 80 °C (bath) for 3–7 h. The solution was passed through a chloroform-filled aluminum oxide pad (~5 g), the support was washed with chloroform (~150 mL), and the volatile products were removed under reduced pressure. Purification of the crude compound by flash column chromatography (silica gel; mobile phase for **21**, **25**, and **27**: pentane/toluene/EtOAc, 40:50:10; mobile phase for **22**–**24** and **26**: toluene) gave target haloesters **21**–**27** (purity >99%, ^{1}H NMR spectroscopy).

1-Oleoyl-2-acetyl-3-chloro-*sn*-glycerol (21): Obtained from **4** (0.447 g, 1.00 mmol) and acetic acid (0.343 mL, 6.00 mmol) after 7 h. Yield: 0.334 g (80%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.60. $[\alpha]_D^{20}$ = +1.28 (*c* = 9.50, $CHCl_3$). $C_{23}H_{41}ClO_4$ (417.02): calcd. C 66.24, H 9.91, Cl 8.50; found C 66.30, H 9.85, Cl 8.53.

1-Chloro-2-palmitoyl-3-oleoyl-*sn*-glycerol (22): Obtained from **5** (0.447 g, 1.00 mmol) and palmitic acid (1.54 g, 6.00 mmol) after 6 h. Yield: 0.582 g (95%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.68. $[\alpha]_D^{20}$ = –2.06 (*c* = 8.49, $CHCl_3$). $C_{37}H_{69}ClO_4$ (613.39): calcd. C 72.45, H 11.34, Cl 5.78; found C 72.50, H 11.30, Cl 5.80.

1,2-Dioleoyl-3-bromo-*sn*-glycerol (23): Obtained from **6** (0.492 g, 1.00 mmol) and oleic acid (1.90 mL, 6.00 mmol) after 5 h. Yield: 0.636 g (93%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.70. $[\alpha]_D^{20}$ = +2.97 (*c* = 7.71, $CHCl_3$); ref.[6] $[\alpha]_D^{20}$ = +2.9 (*c* = 10,

$CHCl_3$). $C_{39}H_{71}BrO_4$ (683.88): calcd. C 68.49, H 10.46, Br 11.68; found C 68.55, H 10.51, Br 11.72.

1-Bromo-2,3-dioleoyl-*sn*-glycerol (24): Obtained from **7** (0.492 g, 1.00 mmol) and oleic acid (1.90 mL, 6.00 mmol) after 5 h. Yield: 0.629 g (92%, colorless oil). $[\alpha]_D^{20}$ = –2.90 (*c* = 9.92, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **23**.

1-Oleoyl-2-acetyl-3-iodo-*sn*-glycerol (25): Obtained from **8** (0.539 g, 1.00 mmol) and acetic acid (0.343 mL, 6.00 mmol) after 4 h. Yield: 0.472 g (93%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.64. $[\alpha]_D^{20}$ = +3.86 (*c* = 9.72, $CHCl_3$). $C_{23}H_{41}IO_4$ (508.47): calcd. C 54.33, H 8.13, I 24.96; found C 54.40, H 8.09, I 25.03.

1-Iodo-2-palmitoyl-3-oleoyl-*sn*-glycerol (26): Obtained from **9** (0.539 g, 1.00 mmol) and palmitic acid (1.54 g, 6.00 mmol) after 3 h. Yield: 0.670 g (95%, colorless oil). R_f (pentane/toluene/EtOAc, 40:50:10) = 0.77. $[\alpha]_D^{20}$ = –3.62 (*c* = 10.28, $CHCl_3$). $C_{37}H_{69}IO_4$ (704.85): calcd. C 63.05, H 9.87, I 18.00; found C 63.11, H 9.80, I 18.05.

1-*O*-Hexadecyl-2-acetyl-3-chloro-*rac*-glycerol (27): Obtained from **10** (0.407 g, 1.00 mmol) and acetic acid (0.343 mL, 6.00 mmol) after 6 h. Yield: 0.305 g (81%, amorphous white solid); R_f (pentane/toluene/EtOAc, 40:50:10) = 0.62. $C_{21}H_{41}ClO_3$ (377.00): calcd. C 66.90, H 10.96, Cl 9.40; found C 66.83, H 11.00, Cl 9.35.

Supporting Information (see footnote on the first page of this article): Characterization of compounds **4**–**27**.

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