O-Silylated C3-halohydrins as a novel class of protected building blocks for total, regio- and stereocontrolled synthesis of glycerolipid frameworks†

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We propose *O*-silylated C3-halohydrins [1(3)-*O*-silyl-2-*O*-acyl-, 1,2(2,3)-*O*-bis(silyl)-, and 1(3)-*O*-acyl-2-*O*-silyl-3(1)-halo-*sn*-glycerides] as new chirons in the total synthesis of glycerolipid constructs. These are efficiently producible *via* opening of the oxirane ring of the corresponding glycidyl derivatives and permit (i) displacement of the iodine by a requisite carboxylate in the presence of *O*-triisopropylsilyl (*O*-TIPS), *O*-*tert*-butyldimethylsilyl (*O*-TBDMS), and *O*-acyl substituents; (ii) selective acylation across an appropriate silyloxy system [*e.g.*, *O*-TBDMS or *O*-triethylsilyl (*O*-TES)] of monoesterified haloglycerides; (iii) direct exchange of an *O*-silyl protection (*e.g.*, *O*-TBDMS or *O*-TIPS) for a trichloroacetyl group; (iv) conversion of a terminal TBDMS group into the corresponding trifluoroacetate without affecting *O*-TIPS-, *O*-acyl- and iodo functions. The above transformations secure flexible routes to a variety of otherwise difficult-to-access key-intermediates [*e.g.*, 1,2(2,3)-*O*-bis(acyl)-3(1)-trichloroacetyl-, 1,3-*O*-bis(acyl)-2-trichloroacetyl-, 1,2(2,3)-*O*-bis(acyl)-3(1)-*O*-TBDMS/TIPS-, 1,3-*O*-bis(acyl)-2-*O*-TIPS/TBDMS-, 1(3)-*O*-acyl-2-*O*-TIPS-, 1,2(2,3)-*O*-bis(acyl)-3(1)-iodo-*sn*-glycerols, *etc.*] and lend themselves to a powerful methodology for the preparation of di- and triacylglycerols as well as glycerol-based cationic lipids. The reactions involved are entirely regio- and stereospecific, avoid acyl migration, and can provide target compounds with a chosen absolute configuration from a single synthetic precursor.

1. Introduction

The ever-increasing experimental evidence that glycerolipids might be a pivotal regulatory element implicated in normal cell function and disease,[1] made this class of biomolecules a focal point of scientific inquiry in once divergent fields of nucleic acid,[2] carbohydrate,[3] and lipid research,[4-7] relevant to clinical diagnostics[8] and rational drug design.[9,10]

Naturally occurring 1,2-*O*-diacyl-*sn*-glycerols (1,2-DAGs) occupy an important position in this regard as they have recently been shown to govern the activity of particular protein families [*e.g.*, protein kinase C (PKC), protein kinase D (PKD), RasGRP, the chimaerins, Unc-13, *etc.*][11] involved in a wide range of vital physiological phenomena *via* signal transduction pathways.[12] Growing interest in lipid mediators concerns site-terminal isomers of 1,2-DAGs as well, namely 1,3-*O*-diacyl-*sn*-glycerols (1,3-DAGs), in view of their distinctive role as endogenous vehicles for transporting essential fatty acids through intestinal mucosa[13] or biomodulators *per se*.[14] Such structurally defined DGs are valuable precursors to triacylglycerols (TAGs)[15,16] or related isosteres (*e.g.*, phospholipids,[5,17,18] cationic lipids,[19,20] and others[9]) and have attracted much attention as micromolecular vectors for either gene transfection[21] or organ-addressed delivery of contrast agents,[8,22] therapeutics,[23] antioxidants,[24,25] and others.[26] In this context, availability of appropriate chemistry allowing flexible derivatization of the glycerol skeleton or parent frameworks is crucial when aiming at new glycerolipid analogues of biochemical and pharmacological relevance.[9,27,28]

While our recent research in the aforementioned field resulted in an efficient triester approach to a stereospecific preparation of DGs and TAGs,[29] the method developed has some limitations. Firstly, the synthetic protocol relied on configurationally pure 1(3)-monoacyl-*sn*-glycerols [1(3)-MAGs], which are often difficult to obtain by means of conventional methods[30,31] and show high propensity towards racemization.[31-33] Secondly, since the two primary carbinol groups of the glycerol backbone are diastereotopic,[34] it precludes admission to both enantiomers of 1,3-DAGs and TAGs, including regioisomeric 1,2(2,1)-DAGs, from one generic C3-unit. Thirdly, the methodology involved derivatization of intermediary 1(3)-*O*-acyl-3(1)-*O*-silyl-*sn*-glycerols and thus access to other glycerolipid analogues, as for example, cationic amphiphiles that are of high demand in gene therapy,[35] is restricted.

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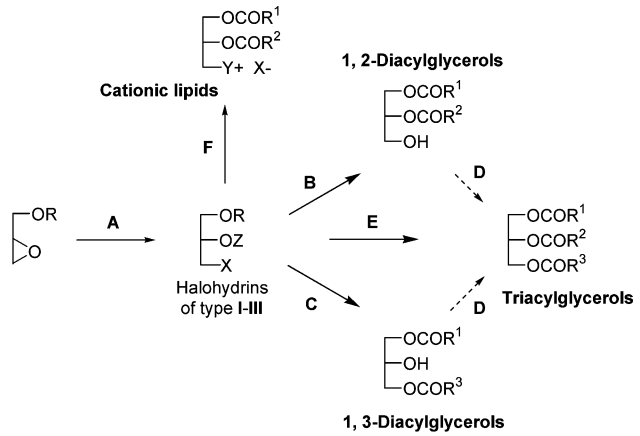
† Electronic supplementary information (ESI) available: Mechanistic insights into a trifluoroacetate anion/4-*N*,*N*-dimethylaminopyridine-assisted synthesis of C2-*O*-acylated- (**7**–**11**, **61**) and C2-*O*-silylated (**12**–**19**) C3-vicinal halohydrins from glycidyls (**1**–**6**). Selective trifluoroacetylation across *tert*-butyldimethylsilyloxy systems of 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-iodo- (**13**) or -3-*O*-acyl-*sn*-glycerols (**26**, **27**) as mediated by trifluoroacetic anhydride in the presence of methanol. The incidence of long-range acyloxy migration during silver trifluoroacetate-promoted replacement of halogen in 1-oleoyl-2-*O*-*tert*-butyldimethylsilyl-3-iodo-*sn*-glycerol (**15**). Preparative details of transformations and characteristics of compounds not shown in the Experimental section. Analytical criteria for assessing regiochemistry of the preparations by high-resolution ^{1}H and ^{13}C NMR spectroscopy. ^{1}H- and ^{13}C NMR data for compounds **7**–**63**. See DOI: 10.1039/b915533c

To address these problems, we report here on three types of *O*-silylated C3-halohydrin derivatives **I**–**III** (Scheme 1) that, to our knowledge, find no literature precedents as building blocks for regio- and stereospecific construction of glycerolipids. Unlike other glyceride precursors,[5] **I**–**III** combine stability under a wide range of reaction conditions with susceptibility to selected reagents (*e.g.*, carboxylate, tetra-*n*-butylammonium halide (Bu_4NX)–trimethylsilyl halide (TMSX)–carboxylic acid anhydride (CAA),[36] $Et_3N{\cdot}3HF$–trichloroacetic anhydride (TCAA),[37] *etc.*). These permit introduction of various acyloxy moieties at *sn*-C1-, *sn*-C2-, and *sn*-C3-centres on the glycerol skeleton in a strictly chemo- and regioselective manner without exposure of a free hydroxyl function.



R, Z = acyl or silyl; R^1, R^2, R^3 = alkyl or phenyl; X = I, Br or Cl

Type **I**: R = silyl; Z = acyl; Type **II**: R = silyl; Z = silyl; Type **III**: R = acyl; Z = silyl;

Y = N

Scheme 1

Since the synthons **I**–**III** are accessible in high yields and under mild reaction conditions from readily available, homochiral glycidyl substrates in a way that also eradicates constraints of existing procedures for converting either secondary alcohols into sterically hindered silyl ethers[38] or silyl-protected glycidols to C2-*O*-acylated C3-vicinal halohydrins,[39] the chemistry as a whole delineates a novel strategy for total, regio- and stereocontrolled syntheses of 1,2(2,3)-DAGs (route B), 1,3-DAGs (route C), structured TAGs (routes D or E), and cationic lipids (route F) (Scheme 1).

2. Results and discussion

Pertinent to the scope and generality of the synthetic objectives outlined in Scheme 1, we required distinct molecular targets that have already been synthesized in an independent way and are known to be highly predisposed to acyl migration, transesterification, hydrolysis, *etc.*, to evaluate the efficiency and mildness of the reaction conditions employed.

In light of the above, a chemically labile 1-oleoyl-2-acetyl- (OAG) and 1-acetyl-2-oleoyl-*sn*-glycerol (AOG), their 1,3-*sn*-isomers or triester isosters (*e.g.*, bearing acetyl, palmitoyl and oleoyl fragments), which are also known as exogenous effectors of PKC[40,41] and Ca^{2+} mobilizing agents,[42] appeared as excellent candidates for this purpose. Another argument justifying this choice of substrates was that identification of regioisomeric species in these instances could be done by ^1H and ^{13}C NMR spectroscopy,[29] without recourse to the enzymatic or chemo-enzymatic analytical techniques often needed for structure elucidation of long-chain triacylglycerols[43,44] lacking as a rule detectable optical activity[16,45] and characteristic spectral features.[46]

Synthesis of halohydrins of types I, II, and III (route A in Scheme 1 and Scheme 2)

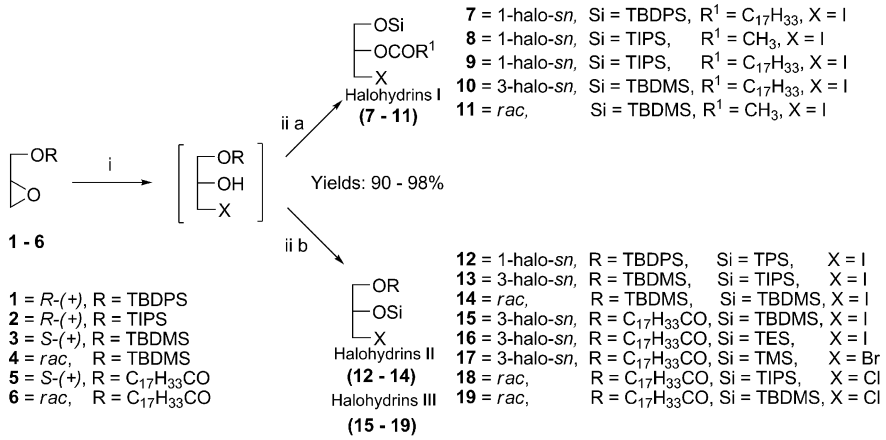
At the crux of the stereospecific synthesis of mixed-acid DGs, TAGs or related conjugates is the need to generate and maintain chirality of a glycerol unit during its sequential derivatization to allow the acyl residues to be introduced at *sn*-1-, *sn*-2-, and *sn*-3-positions.[7,15] This has always been problematic when using acetal-[7,15] or oxirane-derived[30,47] C3-synthons during glycerolipid construction.[5,16] It is noteworthy that access to both enantiomers from these types of classic building blocks[6,48] usually requires using two different starting materials.[5,7,15,18]

The above situation turned our attention to enantiopure mono- and bis(silylated) C3-vicinal halohydrins as alternative glyceride precursors. Unlike their acetal- and oxirane counterparts, that are highly susceptible to racemization/solvolysis also upon storage,[49] the combination of silyl and halogen functionalities should (i) confer stability to a molecule and prevent migration of a fatty acid radical if present; (ii) contribute to differentiation of the two primary carbinol groups since conversion of silyloxy-,[36,37] hydroxyl-,[50] and halide[47,51] systems into a variety of carboxylates proceeds *via* chemically independent routes. As to reactivity of halohydrins, iodo derivatives appeared to be superior to their less reactive chloro-[47] and bromo-homologues[44,51] that typically require more forcing conditions (*e.g.*, elevated temperature or the use of highly polar solvents) to effect a reaction with nucleophiles.[19,52]

Since 1(3)-*O*-silyl- and 1(3)-*O*-acyl-3(1)-halo-*sn*-glycerols are directly obtainable in virtually quantitative yields from glycidyl precursors,[53] we became interested in the development of an efficient protocol for their *in situ* transformation into the respective 1(3)-*O*-silyl-2-*O*-acyl-, 1,2(2,3)-*O*-bis(silyl)-, and 1(3)-*O*-acyl-2-*O*-silyl-3(1)-halo-*sn*-derivatives (preferably iodides) of significance to the present studies. Our previous findings that (i) tetra-*n*-butylammonium trifluoroacetate (TBATFA) represented the only by-product in the reaction mixture after opening of the oxirane ring of glycidyls with trifluoroacetic acid (TFA) in the presence of a halide anion,[53] and (ii) that treatment of TBATFA and acyl-/or silyl chlorides in chloroform with 4-DMAP resulted in powerful acylating-/or silylating system (see ESI, Section 1), provided additional strong rationale for adopting such an approach.

To this end, glycidyls having silyl ether (**1**–**4**) or acyl (**5**, **6**) residues were chosen as representative substrates with different electronic- and steric requirements.

Acid catalyzed opening of the oxirane system of glycidol derivatives **1**–**6** with TFA (1.5 equiv.) in the presence of Bu_4NX (3.0 equiv.)[53] in chloroform at room temperature left cleanly within 5–60 min the expected C3-vicinal haloalkanol (Scheme 2, step i). To produce halohydrins of type **I** (compounds **7**–**11**), the reaction mixture was treated with the requisite acyl chloride (1.50 equiv.) and 4-DMAP (6.0 equiv.) [or pyridine (20.0 equiv.) alternatively applicable to this particular route only] (Scheme 2, step ii a), or for halohydrins of type **II** and **III** (compounds **12**–**14** and **15**–**19**, respectively) with a silyl chloride (3.0 equiv.) needed and



Route A : i) F_3CCOOH (1.5 equiv.)/Bu_4NX (3.0 equiv.), $CHCl_3$, r.t./5 min - 1 h;
ii a) CH_3COCl or $C_{17}H_{33}COCl$ (1.5 equiv.)/4-DMAP (6.0 equiv.) [or pyridine (20.0 equiv.)], $CHCl_3$, r.t./10 - 20 min (ca. 2 h);
ii b) TMSCl, TESCl, TPSCl, TBDMSCl or TIPSCl (3.0 equiv.)/4-DMAP (6.0 equiv.), $CHCl_3$, r.t./5 min - 24 h;

Scheme 2

4-DMAP (6.0 equiv.) (Scheme 2, step ii b). This gave quantitatively and in a strictly chemo- and regioselective way (>99%, ^{1}H and ^{13}C NMR spectroscopy) C2-acylates **7–11** (10–20 min; if pyridine used instead, *ca.* 2 h) and C2-*O*-silyl ethers **12-19** (5 min–1.5 h; for the reaction with TIPSCl, 24 h), which were isolated in 90–98% yields after flash column silica gel chromatography. The chemistry seemed to be rather general as other glycidyl conjugates (*e.g.*, acetyl, arachidonoyl, 4-nitrobenzoyl, hexadecyl or isopropyl; data not shown) also underwent smooth conversion to the analogous 2-*O*-functionalized vicinal chloro-, bromo-, and iodohydrins of types **I–III**. Some mechanistic aspects of these reactions were investigated and shortly discussed in the Supplementary Information (see ESI, Table S1 and Scheme S1).

The formation of haloglycerides **7–10**, **12**, **13**, and **15–17** with defined stereochemistry and the lack of acyl migration (or accumulation of by-products through exchange of a halogen in the C3-unit) are in conformity with a putative mechanism (pathway 2) described in ESI (Scheme S1).

As the increase of steric bulk on silicon renders silyl chlorides progressively less reactive towards secondary alcohols,[54] the strategy depicted in Scheme 2 permits efficient silylation of C3-vicinal haloalkanols at C2, without recourse to forceful reaction conditions.[38]

Having developed a methodology for a one-pot synthesis of halohydrins **7–19** from the corresponding oxirane educts **1–6**, the important question to be addressed next was whether saturated, unsaturated and hydrolytically labile (*e.g.*, trifluoroacetyl or trichloroacetyl) acid-chains can be incorporated in a chemo-, regioselective, and stereospecific manner at a given position within the glycerol framework by acylating directly an incipient hydroxyl group, in the presence of *O*-silyl-, *O*-acyl- and halo-functionalities.

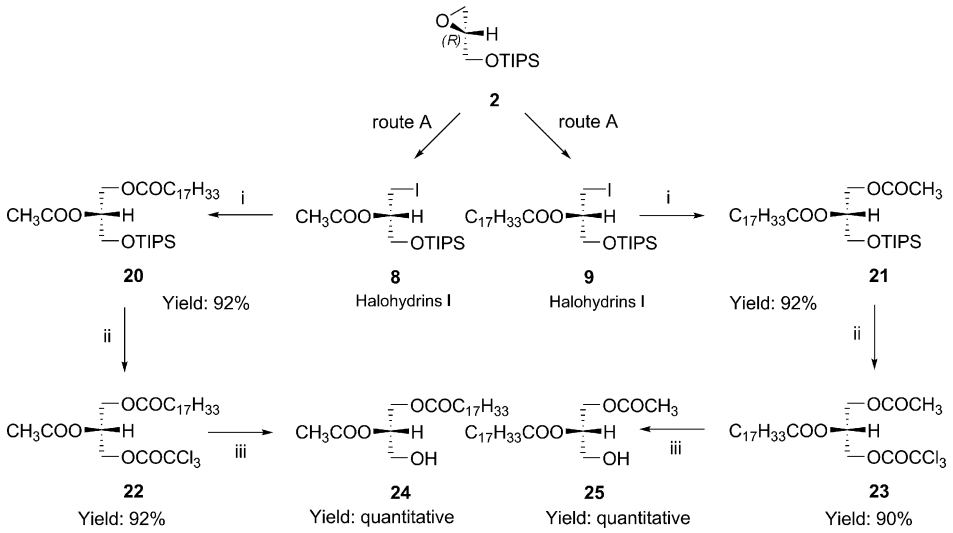
Total synthesis of 1,2(2,1)-*O*-diacyl-*sn*-glycerols from iodohydrins of type I (route B in Scheme 1 and Scheme 3)

Total synthesis of 1,2(2,3)-*O*-diacyl-*sn*-glycerols and derivatives thereof usually makes use of naturally occurring chiral species [*e.g.*, D-mannitol,[7] D- or L-serine,[55] L-glyceric acid,[56] L-erythrulose,[57] or *sn*-glycero-3-phosphocholine[41]] or synthetic building blocks (*e.g.*, glycerol acetals,[15,45,58] various glycidol derivatives,[47,59] and others[5,18]) that can be elaborated by chemical[5,16] or chemoenzymatic[18,60] techniques to an enantiomerically pure 1(3)-monoacyl-*sn*-glycerol [1(3)-MAG] bearing a transient protection at the other primary hydroxyl function.

Regioselective and stereospecific preparation of such key intermediates from the above congeners is a rather tedious task due to separation problems,[45,59,61] low to moderate isolated yields,[45,61,62] and extensive side reactions (*e.g.*, acyl migration, formation of cyclic systems, hydrolysis of an ester function, *etc.*)[31,33,63] that erode stereochemistry. For quaternary ammonium salt-promoted cleavage of the epoxide ring of glycidyl substrates by carboxylic acids,[47,59] harsh reaction conditions and poor regioselectivity of the transformations are the main setbacks of these strategies.

Contrary to these, we show in Scheme 3 that halohydrins of type **I** (compounds **8** and **9**, obtained from one common precursor as in Scheme 2), bearing C2-acetate (**8**) or C2-oleate (**9**) can be efficiently converted into isomeric diglycerides **24** and **25**, respectively.

The reaction sequence commenced with substitution of iodide in **8** and **9** by the corresponding carboxylic acid moiety. This was effected by treatment of halohydrin **8** with tetra-*n*-butylammonium oleate (3.0 equiv.), and **9** with tetra-*n*-butylammonium acetate (3.0 equiv.), in toluene at 80 °C for *ca.* 1.5 h. ^{1}H and ^{13}C NMR spectra of the isolated products (see Experimental) revealed that under these conditions the conversion to the target compounds **20** *vs.* **21** was nearly quantitative and entirely chemo- and regioselective (>99%;) as assessed by the comparative analytical NMR criteria presented in ESI (Section 5). No by-products due to possible acyl migration or dehydroiodination could be detected by means of TLC or ^{1}H and ^{13}C NMR spectroscopy. In all cases, the rates of the reactions were not appreciably affected by the structural features the iodohydrin derivatives (*i.e.* **8** *vs.* **9**) or the attacking carboxylate (*i.e.* oleate *vs.* acetate). Also other alkyl iodides [*e.g.*, methyl iodide, oleyl iodide, 1-*O*-hexadecyl-2-acetyl-3-iodo-*rac*-glycerol, or 1-iodo-2-oleoyl-3-*O*-*tert*-butyldiphenylsilyl-*sn*-glycerol (**7**); data



Route B : i) $Bu_4N^+CH_3COO$- or $C_{17}H_{33}COO$- (3.0 equiv.), toluene, 80 °C/1.5 h;
ii) $Et_3N.3HF$ (2.0 equiv.), $(CCl_3CO)_2O$ (9.0 equiv.), no solvent, 80 °C/2 h;
iii) pyridine (50 equiv.), MeOH (500 equiv.), THF, r.t./2 h.

Scheme 3

not shown] could be quantitatively converted to the corresponding esters.

Since nucleophilic substitution of the iodine atom within these substrates could be carried out using readily available quaternary ammonium carboxylates in a non-polar environment, this eliminated the necessity of using costly[44,51] and poorly soluble in common organic media metal salts of carboxylic acids[44,47,51] deemed as the reagents of limited synthetic utility.[64]

Due to high susceptibility to acyltropy of unprotected 1,2(2,3)-diglycerides[5,32] or during removal of a silyl group from their synthetic precursors,[65] we converted the silyl derivatives **20** and **21** into the corresponding trichloroacetyl derivatives (**22** and **23**, respectively), that can be considered as a convenient storage form for diglycerides.[29,37] To this end the silyl ethers **20** and **21** were treated with trichloroacetic anhydride (TCAA, 9.0 equiv.) and $Et_3N{\cdot}3HF$ (2.0 equiv.) at 80 °C for 2 h to effect quantitatively and in a highly chemo- and regiospecific fashion (>99%, ^1H and ^{13}C NMR spectroscopy) a direct transformation of *O*-TIPS group into trichloroacetates in **22** and **23** (Scheme 3, step ii). These compounds were isolated in 90–92% yields and no decomposition (^1H and ^{13}C NMR spectra; optical activity) could be detected upon storage for several months (–20 °C, under argon).

In addition to a stabilizing effect to labile constructs like **22**, **23**, the importance of having a trichloroacetyl functionality was that this group could be selectively removed even in the presence of acetyl esters. Thus, treatment of trichloroacetates **22** and **23** in THF with pyridine (50 equiv.) and methanol (500 equiv.) at room temperature for 2 h (Scheme 3, step iii), followed by evaporation of volatile products under reduced pressure, afforded OAG (**24**) and the regioisomeric AOG (**25**) of purity >99% (^1H and ^{13}C NMR spectroscopy).

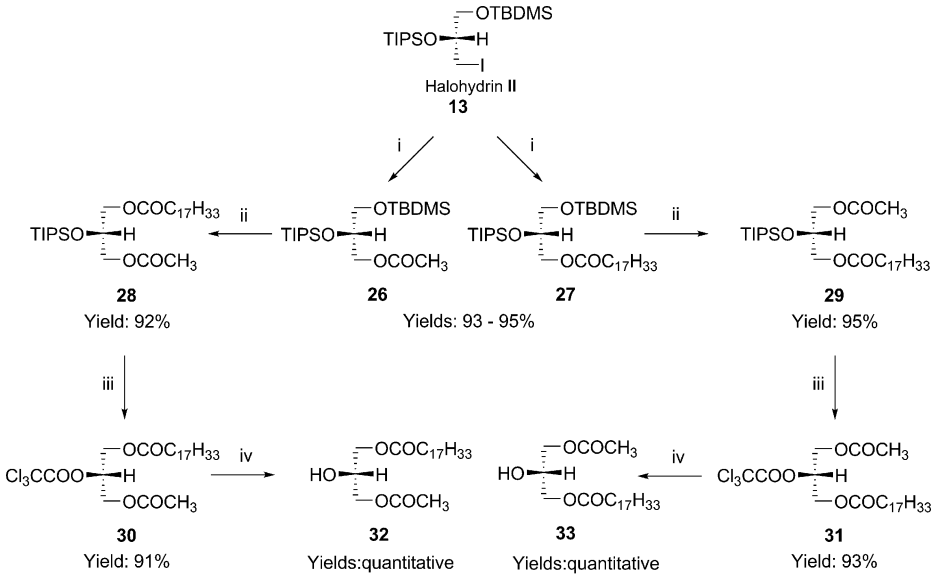
As (*R*) and (*S*)-2-(silyloxymethyl)oxiranes with diverse steric features at silicon are easily prepared from commercially available chiral glycidols,[66] both enantiomers of a 1,2- or 2,3-*O*-diacylglycerol could be accessed by the protocol described above.

Total synthesis of 1,3-*O*-diacyl-sn-glycerols from iodohydrins of type II (route C in Scheme 1 and Scheme 4)

Interchange of two acyl substituents (*e.g.*, acetyl *vs.* oleoyl) at C1- and C3-*sn*-sites of a glycerol unit should produce enantiomeric pairs of the respective 1,3-*O*-diacyl-*sn*-glycerol (*e.g.*, **32** *vs.* **33**), provided that no scission of a C–O bond at C2-stereocenter takes place during the reaction sequence.

Despite its apparent triviality, the concept has not been exploited to any significant extent as a useful approach to stereochemically defined 1,3-DAGs, due to acute problems in regioselective incorporation of individual acyl moieties at primary positions of a glycerol backbone.[5,16] For example, treatment of glycidyl esters with another fatty acid in the presence of a quaternary ammonium salt at 100–110 °C (2–4 h), was shown to produce mixtures of 1,2- and 1,3-*O*-diacylglycerols in erratic proportions.[55] Although advocated as superior to protection–deprotection protocols, this method and its latter modifications[67] suffer from lack of generality and harsh reaction conditions that contribute to formation of transesterification products, acyl migration, epimerization, oxidation, *etc.*[59] One-step methodologies based on esterification of 1-monoglycerides with various acyl donors, seem to be equally inefficient[16] and afford 1,3-diglycerides in low yields (44–46%).[25,42]

These difficulties prompted us to consider 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-iodo-*sn*-glycerol (**13**) as a new building block (halohydrin of type **II**) in the synthesis of 1,3-DAGs (Scheme 4), to permit a direct incorporation of an acyl group into any position of the glycerol skeleton.



Route C : i) $Bu_4N^+CH_3COO$- or $C_{17}H_{33}COO$- (3.0 equiv.), toluene, 80 °C/1.5 h;
ii) Bu_4NBr (2.0 equiv.)/TMSBr (1.5 equiv.)/$(CH_3CO)_2O$ or $(C_{17}H_{33}CO)_2O$ (3.0 equiv.), $CHCl_3$, 80 °C/2 h;
iii) $Et_3N.3HF$ (3.0 equiv.), $(CCl_3CO)_2O$ (12.0 equiv.), no solvent, 80 °C/6 h;
iv) pyridine (50 equiv.), MeOH (500 equiv.), THF, r.t./2 h.

Scheme 4

The first step of the reaction sequence, *i.e.* replacement of the iodide group in halohydrin **13** either by tetra-*n*-butylammonium acetate or oleate (3.0 equiv.) in toluene at 80 °C was uneventful, and afforded in highly chemo- and regiospecific manner (>99%, ^{1}H and ^{13}C NMR spectroscopy) 3-*sn*-monoesters **26** and **27** in 93–95% isolated yields.

Having at the C2 position in **26** and **27** an unreactive *O*-TIPS functionality we attempted to introduce a second acyl group *via* a selective acylation across the terminal *tert*-butyldimethylsilyloxy system using Bu_4NBr–TMSBr–CAA[36] reagent system.

For this purpose, a solution of monoester **26** or **27** and Bu_4NBr (2.0 equiv.) in chloroform was treated at 80 °C with a mixture of oleic or acetic anhydride (3.0 equiv.) and TMSBr (1.5 equiv.) for 2 h. ^{1}H- and ^{13}C NMR spectra revealed that transformation of **26** and **27** into the corresponding 1,3-*O*-diacyl-*sn*-derivative **28** and **29** was practically quantitative and entirely regioselective (>99%). No by-products due to possible intramolecular rearrangements or side reactions involving either the olefinic part of the oleic acid or the *O*-TIPS moiety at C2, were observed.

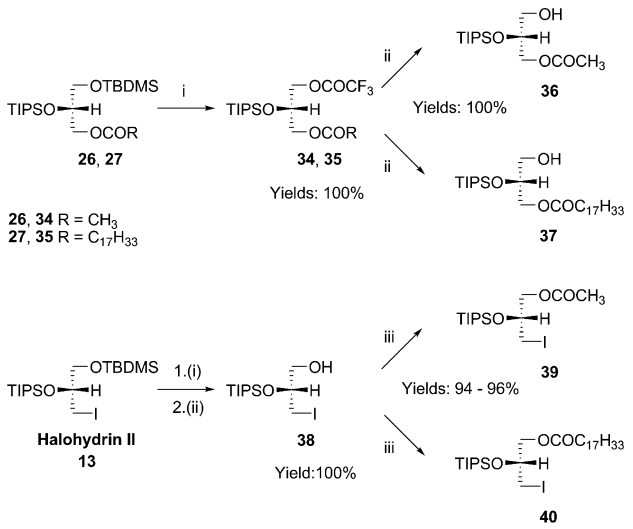
Critical to a successful synthesis of diglycerides **28** and **29** was the fact that a more reactive silyl group (TBDMS) was at the primary position of the glycerol system, while a less reactive one (TIPS), at the C2 centre. Exchanging the positions of TBDMS- and TIPS-groups within **26** or **27** (*e.g.*, to form 1-*O*-triisopropylsilyl-2-*O*-*tert*-butyldimethylsilyl-3-acetyl-/or -3-oleoyl-*sn*-glycerol) led to indiscriminate acylolysis of both *O*-silyl protecting groups under the reaction conditions. Similar results were obtained when 1,2-*O*-bis(*tert*-butyldimethylsilyl)-3-stearoyl-*rac*-glycerol (prepared from halohydrin **14**) was used for the reaction.

In the next step of this synthetic protocol, we replaced *O*-TIPS ethers with trichloroacetate groups (Scheme 3, step iii), by reacting silyl ethers **28** or **29** with trichloroacetic anhydride (12.0 equiv.) in the presence of $Et_3N{\cdot}3HF$ (3.0 equiv.) at 80 °C for 6 h.[29,37] This furnished 2,2,2-trichloroacetates **30** and **31** (isolated yields: 91-93%) in a strictly chemo- and regioselective manner (>99%, ^{1}H- and ^{13}C NMR spectroscopy). Comparison of the optical rotations of **30** *vs.* **31**, ($[\alpha]_D^{20}$ = –0.69 *vs.* $[\alpha]_D^{20}$ = +0.66), with that of the reference 1-oleoyl-2-trichloroacetyl-3-acetyl-*sn*-glycerol ($[\alpha]_D^{20}$ = -0.68),[36] indicated retention of configuration in the C3-unit. These findings were in agreement with a putative mechanism proposed previously for the reactions involving primary silyloxy systems of glycerol.[37]

As for 1,2-*sn*-digycerides, trichloroacetates **30** and **31** could be efficiently converted into unprotected 1,3-*sn*-digycerides **32** ($[\alpha]_D^{20}$ = –0.27) and **33** ($[\alpha]_D^{20}$ = +0.28), respectively, *via* treatment with methanol–pyridine in THF (Scheme 3, step iv). Enantiomeric purity of the isolated compounds was additionally confirmed by conversion to the corresponding Mosher esters,[29] and can serve as a proof of stereochemical integrity within the entire protocol.

In Scheme 5, a useful variant of this method for the preparation of asymmetric of 1,3-DAGs is shown, that involves derivatization of halohydrin **II** precursor **13** (or derived from it 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-*O*-acyl-*sn*-glycerols **26** and **27**) to produce C3-synthons bearing a free hydroxy-function at *sn*-C1 (*e.g.*, **36-38**) or halohydrins of type **III** (compounds **39** and **40**).

Attempted direct transformation of *tert*-butyldimethylsilyl into trifluoroacetyl groups by means of a reagent system we have recently developed [*e.g.*, Bu_4NI (2.0 equiv.)–TFAA (2.0 equiv.)] for trifluoroacetylation of TMS[68] ethers was, unfortunately, unsuccessful due to sluggish reaction (*ca.* 48 h at 80 °C for the completion) and formation 1,2-bis(trifluoroacetyl)-derivatives (7–12%) from **13**, **26** and **27** (^{1}H- and ^{13}C NMR spectroscopy).



i) $(CF_3CO)_2O$ (12.0 equiv.), MeOH (3.0 equiv.), $CHCl_3$, 70 °C/2 h; ii) pyridine (50 equiv.), MeOH (500 equiv.), THF, r.t./30 min; iii) CH_3COCl or $C_{17}H_{33}COCl$ (2.0 equiv.), pyridine (20.0 equiv.), $CHCl_3$, r.t./2 h.

Scheme 5

After exploring various reaction conditions, the best results were achieved when **13**, **26** or **27** was reacted with trifluoroacetic anhydride (12.0 equiv.) in chloroform at 70 °C for 2 h in the presence of methanol (3.0 equiv.). Removal of the volatile products under reduced pressure provided positionally homogeneous (purity >99%, ^{1}H- and ^{13}C NMR spectroscopy) the corresponding trifluoroacetyl esters without supplementary chromatography (Scheme 5, step i). This method of trifluoroacetylation across a silyloxy system worked well also for other TBDMS-protected compounds [*e.g.*, iodohydrins of type **10**, 4-chloro-1-(*O*-TBDMS)-butanol, *etc.*] or C2-*O*-silyl ethers (**16** and **17**, data no shown). The produced trifluoroacetyl derivatives could be used as a storage form for these precursors, or be converted into compounds **36–38** with a free hydroxyl function (Scheme 5, step ii) by treatment with pyridine–methanol in THF at room temperature for 30 min (purity >99%; ^{1}H- and ^{13}C NMR spectroscopy).

Due to the strictly quantitative character of both incorporation (step i) and cleavage of a trifluoroacetyl group (step ii), the conversion of the starting materials such as **13**, **26** and **27** into the suitably modified precursors of 1,3-DAGs (*e.g.*, **36–38** or **39**, **40**) could be executed as a one-pot procedure, and then subjected to additional functionalization as shown in Scheme 5 (step iii).

It is worth noting that replacement of TFAA by trichloroacetic anhydride (TCAA) resulted in very slow reaction (after 8 days, conversion ~80%). For some mechanistic aspects of the trifluoroacetylation reaction across the silyloxy system, see ESI (Scheme S2).

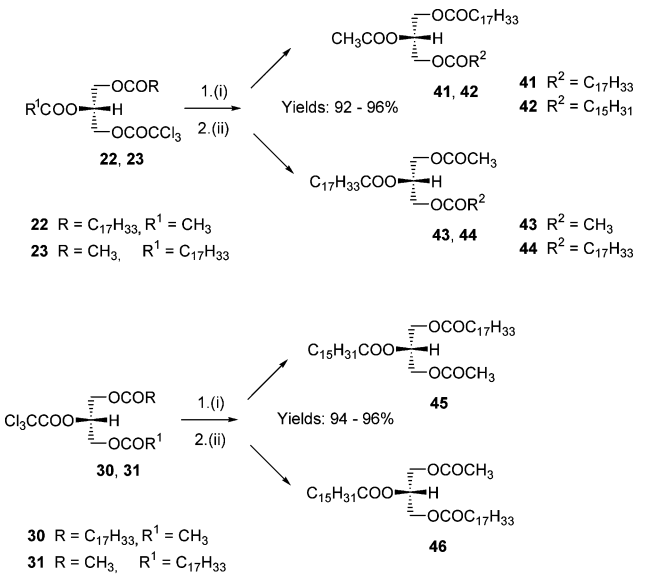
Synthesis of mixed-acid triacylglycerols from diglyceride precursors (route D in Scheme 1 and Scheme 6) or from iodohydrins I and III (route E in Scheme 1 and Scheme 7)

The already discussed problems associated with a regioselective and stereospecific incorporation of two different acyl substituents into a glycerol unit apply also to the synthesis of structured triacylglycerols (STGs). For example, methods relying on a traditional chiral pool of 3,4-isopropylidene-D-mannitol[7] and 1,2-isopropylidene-*sn*-glycerol[15] require at the least ten protection–deprotection steps to produce a mixed-chain glyceryl triester. While a one-pot acylolytic cleavage of esterified glycerol acetals,[69] as well as a consecutive esterification of monoglycerides[24,25,42,70] have been recently proposed as less arduous approaches to STGs, these methodologies often suffer from extended reaction time (1–3 days), mediocre regioselectivity, and afford the desired compounds usually in poor to moderate yields (7–68%). Although opening of the epoxide ring of glycidyl esters with reagent systems consisting of LiBr–carboxylic acid anhydrides[51] or LiBr–oleic anhydride–benzyltributylammonium bromide,[44] followed by a caesium carboxylate effected acidolysis of bromine in the resulted 3-bromo-1,2-propanediol diacylates, has been suggested to provide a short entry to STGs, the chemistry involved does not prevent completely formation of the isomeric products.[44]

Within the framework of the presented here synthetic methodology, triglycerides can be prepared from suitable diglycerides precursors (Scheme 6), or directly from halohydrins **I** or **III** (Scheme 7).

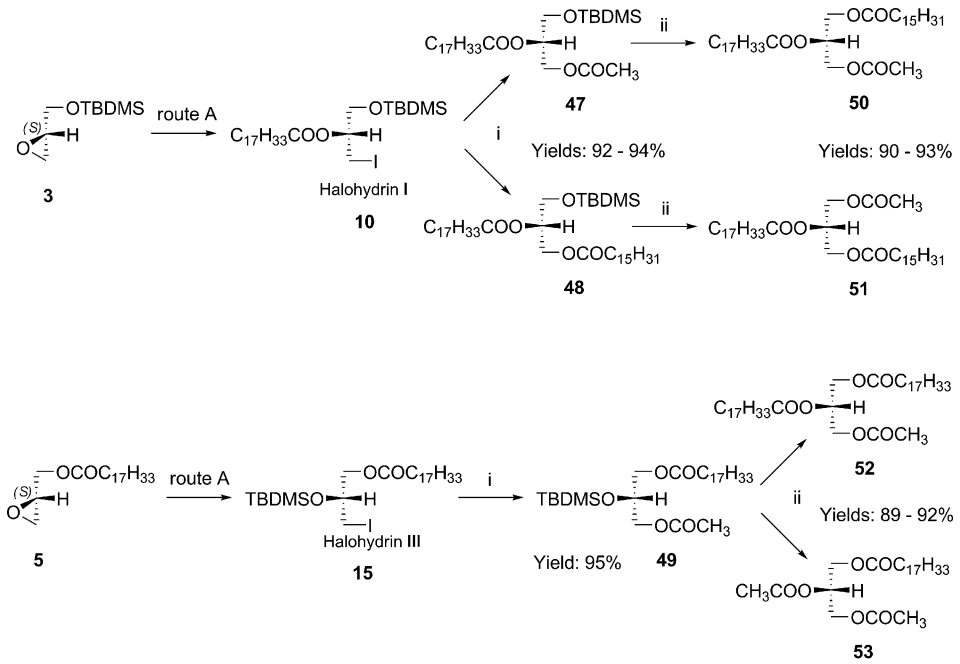
For the first approach, the most suitable precursor seemed to be 1,2-*O*-diacyl-3-trichloroacetyl- (*e.g.*, **22**, **23**) or 1,3-*O*-diacyl-3-trichloroacetyl-*sn*-glycerols (*e.g.*, **30**, **31**), easily accessible from *O*-silylated glycidyl **2** or iodohydrin **13**, as described above (Scheme 3 and Scheme 4).

Introduction of the third fatty acid moiety to diglycerides **22**, **23** or **30**, **31**, involved two reaction steps: (i) removal of a trichloroacetate moiety with methanol–pyridine and (ii) acylation of an unprotected diglyceride with an acyl chloride (Scheme 6). These, produced quantitatively and in a regioselective way (>99%, ^{1}H- and ^{13}C NMR spectroscopy) the target triacylglycerols **41–46** in isolated 92–96%.



Route D : i) pyridine (50 equiv.), MeOH (500 equiv.), THF, r.t./2 h; ii) CH_3COCl, $C_{15}H_{31}COCl$ or $C_{17}H_{33}COCl$ (2.0 equiv.), pyridine (20.0 equiv.), $CHCl_3$, r.t./2 - 3.5 h.

Scheme 6



Route E : i) $Bu_4N^+CH_3COO$-, or $C_{15}H_{31}COO$- (3.0 equiv.), toluene, 80 °C/1.5 h;
ii) Bu_4NBr (2.0 equiv.)/TMSBr (1.5 equiv.)/$(CH_3CO)_2O$, $(C_{15}H_{31}CO)_2O$ or $(C_{17}H_{33}CO)_2O$ (3.0 equiv.), $CHCl_3$, 80 °C/2 - 7 h.

Scheme 7

One should note that the above approach can provide also a convenient access to the various triglyceride derivatives bearing a reporter or a new functional group (*e.g.*, fluorescent, photoactivable, isotopic or spin-labelled probes, phosphoester headgroups, *etc.*)[5,9,18,28,30] at the predetermined position of the glycerol moiety.

Synthesis of triglycerides from halohydrins type **I** (*e.g.*, **10**) and **III** (*e.g.*, **15**) is shown in Scheme 7.

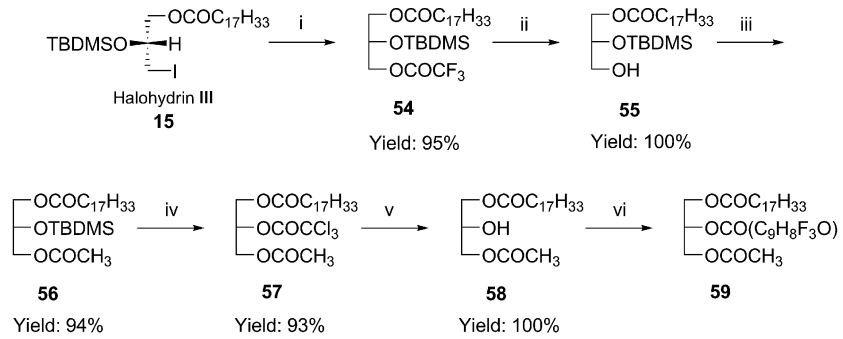
The protocol seems to be more versatile than that making using of diglyceride intermediates (Scheme 6) and can provide access to enantiomerically pure triglycerides from a single chiral halohydrin precursor. This was demonstrated in a reaction sequence in Scheme 7 for the synthesis of enantiomeric triglycerides **50** and **51**, starting from the same halohydrin **I** precursor (compound **10**). The strategy involved (i) displacement of the iodide in **10** by means of either tetra-*n*-butylammonium acetate or tetra-*n*-butylammonium palmitate to produce diglycerides **47** and **48** in 92–94% isolated yields, and (ii) treatment of silyl ethers **47** and **48** and Bu_4NBr (2.0 equiv.) in chloroform at 80 °C (pressure tube) for 2 h with, respectively, palmitic or acetic acid anhydride (3.0 equiv.) and TMSBr (1.5 equiv.) to afford triglycerides **50** and **51** (Scheme 7). ^{1}H- and ^{13}C NMR analysis indicated, that under the reaction conditions conversion of **47** and **48** to the final products was nearly quantitative (90–93% yields after flash column silica gel chromatography) and provided enantiomerically pure 1-palmitoyl-2-oleoyl-3-acetyl-*sn*-glycerol **50** ($[\alpha]_D^{20} = -0.74$) and 1-acetyl-2-oleoyl-3-palmitoyl-*sn*-glycerol **51** ($[\alpha]_D^{20} = +0.76$).

In the synthesis of triglycerides from halohydrins of type **III** (compound **15** in Scheme 7), acylation across the silyloxy system of glycerol effected by Bu_4NBr–CAA–TMSBr[36] occurred at the C2 chiral centre, and thus also stereochemistry of this step was of interest. As for the reactions involving halohydrins of type **I** (Scheme 7), the formations of STGs **52** and **53** (89–92% isolated yields) was entirely chemo- and regioselective (>99%, ^{1}H- and ^{13}C NMR spectroscopy). In addition, by comparing optical rotations of 1,2-dioleoyl-3-acetyl- **52** ($[\alpha]_D^{20} = -0.66$) and 1-oleoyl-2,3-diacetyl-*sn*-glycerol **53** ($[\alpha]_D^{20} = -1.28$) with those of the reference compounds[29] and 1-acetyl-2,3-dioleoyl-*sn*-glycerol **44** ($[\alpha]_D^{20} = +0.70$) (this work) we could conclude that replacement of the silyloxy group in **49** by an acyl function (Scheme 7, step ii) occurred with retention of configuration at C2.

Finally, we were interested in conversion of halohydrins of type **III** (1-oleoyl-2-*O*-*tert*-butyldimethylsilyl-3-iodo-*sn*-glycerol, **15**) into a useful intermediate **55** (Scheme 8), which upon acylation with common acyl chlorides (step iii) and the subsequent derivatization (steps iv and v in Scheme 8) would delineate a complementary approach to 1,3-diacyl-*sn*-glycerols (*e.g.*, compound **58**) and ultimately, STGs (compound **59**, Scheme 8). Relevant to this goal, the presence of the TBDMS group at the glycerol C2-position was believed to secure the stereochemical integrity of **15** during displacement of the iodine (step i) and prevent acyl migration after exposure of a free hydroxyl function in **55**.

Unfortunately, somewhat unexpectedly we experienced problems in the first reaction step, namely, the replacement of iodide in **15** by a trifluoroacetyl function. In contrast to the tetra-*n*-butylammonium carboxylates investigated (Schemes 3, 4 and 7), tetra-*n*-butylammonium trifluoroacetate was essentially unreactive in nucleophilic substitution in **15**, and we had to use silver trifluoroacetate as an alternative reagent.

The reaction sequence in Scheme 8 was very efficient but all synthesized compounds **54–58** consistently lacked any ap-



Step (i) CF_3COOAg (3.0 equiv.), toluene, 60 °C/2 h; step (ii) pyridine (50 equiv.)/MeOH (500 equiv.), THF, r.t./30 min; step (iii) CH_3COCl (2.0 equiv.)/pyridine (20 equiv.), $CHCl_3$, r.t./2 h; step (iv) $Et_3N.3HF$ (3.0 equiv.)/$(CCl_3CO)_2O$ (12.0 equiv.), no solvent, 80 °C/2.5 h; step (v) pyridine (50 equiv.)/MeOH (500 equiv.), THF, r.t./2 h; step (vi) *R*-(-)-MTPA-Cl (2.0 equiv.)/pyridine (20 equiv.), $CHCl_3$, r.t./20 h.

Scheme 8

preciable optical activity. Conversion of the final product **58** into the Mosher ester **59** (step vi, Scheme 8) revealed (^{1}H and ^{13}C NMR spectroscopy) that **58** represented virtually an equimolar mixture of 1-oleoyl-3-acetyl-*sn*-glycerol and its 1-acetyl-3-oleoyl-*sn*-enantiomer. The observed epimerization occurred most likely during the replacement of iodine in **15** by silver trifluoroacetate, probably due to a transient generation of symmetrical 1,3-dioxonium cation and 1,3-acyloxy group migration (see, ESI and Scheme S3 for some mechanistic details). This observation pointed also to the advantage of using tetra-*n*-butylammonium carboxylates *vs.* metal carboxylates[44,71] in the reactions involving nucleophilic substitution in halohydrins.

A short synthesis of cationic lipids from halohydrins of type I and III (route F in Scheme 1 and Scheme 9)

To demonstrate the synthetic utility of halohydrins as key intermediate in the synthesis of a glycerolipid framework, we prepared two cationic lipids from halohydrins of type **I** and **III**. Cationic lipids based on glyceride frameworks are gaining increasing importance as alternative synthetic gene delivery vectors to recombinant viruses,[20,72] or as agents for biochemical and medicinal intervention.[73] Quaternary ammonium salts of diacylglycerols, such as *N*-[1-(2,3-dioleoyloxy)propyl]-*N*,*N*,*N*-trimethylammonium methyl sulfate (DOTAP)[74] and its analogues,[19] have attracted particular attention in this respect. Due to the presence of enzymatically labile acyloxy functionalities, this class of cationic amphiphiles exhibits a better transfection profile and reduced cytotoxicity compared to classical systems.[75,76] It was demonstrated that the presence of the iodide counterion increased significantly transfection activity,[75,77] while the replacement of an alkyl ammonium head group by a pyridinium moiety, resulted in lower cytotoxicity and increased tissue penetration ability.[78]

In Scheme 9, the synthesis of two cationic lipids, pyridinium derivative **62** [(±)-*N*-(1-oleoyl-2-acetyl-3-propyl)pyridinium iodide] and **63** [(-)-*N*-(1-oleoyl-2-palmitoyl-3-propyl)pyridinium iodide] as analogues of DOTAP, is depicted.

The first step of the reaction sequence involved Bu_4NI–TMSI-mediated acylation of halohydrins **I** (compound **11**) or **III** (compound **16**) with an appropriate carboxylic acid anhydride, (3.0 equiv.) and resulted in regioisomerically homogeneous (>99%, ^{1}H and ^{13}C NMR spectroscopy) iodohydrins **60** and **61** (isolated in 92–94% yields after flash column silica gel chromatography). Trifluoroacetic acid-catalysed opening of the oxirane system of glycidyl oleate (**5**) in the presence of iodide,[53] followed by treatment with palmitoyl chloride [Scheme 9, steps i(a) and i(b)] represents a complementary strategy to a homochiral 1-oleoyl-2-palmitoyl-3-iodo-*sn*-glycerol **61**.

As a final stage of this synthetic protocol, the obtained *O*-bis(acylated) C3-iodohydrins **60** and **61** were reacted under argon with pyridine at 80 °C for *ca.* 18 h to give the target pyridinium cation lipids **62** and **63** in 87–90% isolated yields.

In conclusion, we have developed an efficient chemistry for producing halohydrins of type **I**–**III** (Scheme 1) as a novel class of protected chirons of broad interest to regio- and stereocontrolled synthesis of diglycerides (*e.g.*, **24**, **25**, **32** or **33**), triglycerides (*e.g.*, **22**, **23**, **30**, **31**, **41**–**46**, **50**–**53**) and glycerol backbone-derived cationic lipids (*e.g.*, **62**, **63**).

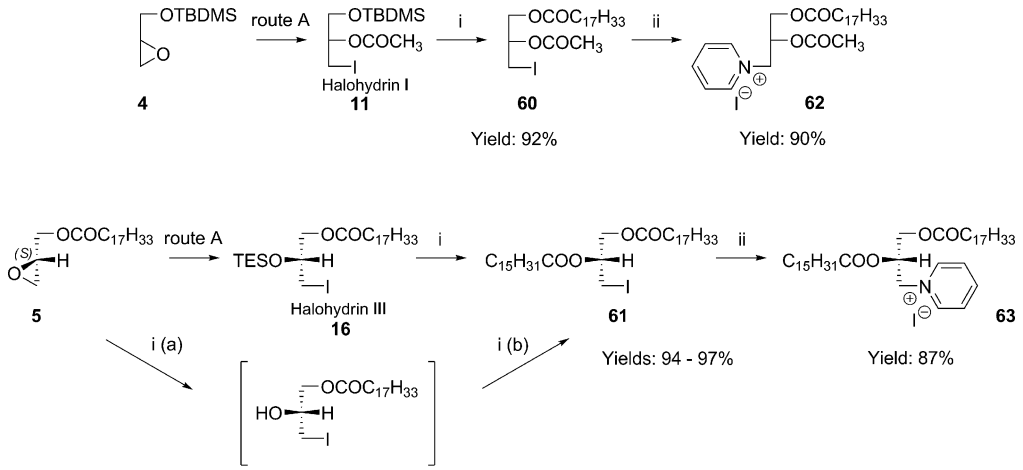
The main advantages of halohydrins of type **I**–**III** as key intermediates in glycerolipid synthesis are: (i) facile accessibility from suitable glycidol derivatives, (ii) stability towards decomposition or intramolecular rearrangements, (iii) possibility for highly regioselective and stereospecific introduction of diverse acid-chains at any position of a glycerol framework without exposure of a free hydroxyl group, (iv) possibility to obtain enantiomeric pairs of 1,3-DAGs and TAGs from one homochiral precursor.

This new strategy is high yielding, minimizes the number of synthetic/purification operations, and can easily be scaled up. It seems to be rather general and can be used for the synthesis of glyceride derivatives of relevance to biochemical or biophysical studies or to other applications where regioisomeric-/isosteric forms of chiral lipid mediators are required.

3. Experimental

3.1. General

All reagents were commercial grade (Fluka, Lancaster, Merck, Sigma) with purity >98% and were used as provided without



i) Bu_4NI (2.0 equiv.)/TMSI (1.5 equiv.)/$(C_{17}H_{33}CO)_2O$ or $(C_{15}H_{31}CO)_2O$ (3.0 equiv.), $CHCl_3$, 80 °C/30 min - 2 h;
ii) Pyridine (30.0 equiv.), 80 °C/18 h.

Alternative synthesis of **61**: i (a) F_3CCOOH (1.5 equiv.)/Bu_4NI (3.0 equiv.), $CHCl_3$, r.t./5 min;
i (b) $C_{15}H_{31}COCl$ (1.5 equiv.)/4-DMAP (6.0 equiv.), $CHCl_3$, r.t./ca. 10 min.

Scheme 9

further purification. Solvents were dried and distilled prior to use according to standard protocols.[79] Reaction conditions were kept strictly anhydrous unless stated otherwise.

Progress of the reactions was monitored by analytical thin-layer chromatography on pre-coated glass plates of silica gel 60 F_{254} (Merck). The spots were visualized using the commercially available 3.5% molybdatophosphoric acid spray reagent (Merck) or 50% sulfuric acid followed by heating at 140 °C. Column chromatography was carried out on silica gel 60 (70–230 mesh ASTM, Merck). For preparative parameters of transformations not shown in the main body text, see ESI (Section 4).

^1H and ^{13}C NMR spectra were recorded on a Varian 400 MHz machine and chemical shifts are reported in ppm relative to TMS. The assignment of proton and carbon resonances of **1–63** was done on the basis of known or expected chemical shifts in conjunction with ^1H–^1H, ^1H–^{13}C, and DEPT correlated NMR spectroscopy. In certain instances, only the most informative parts of ^1H and ^{13}C NMR spectra of known compounds,[29,68,80] were provided for the sake of convenience.

Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter. The melting points were determined on a Kofler melting point apparatus and are uncorrected.

Tetra-*n*-butylammonium acetate was purchased from Aldrich. Tetra-*n*-butylammonium palmitate, tetra-*n*-butylammonium oleate, and tetra-*n*-butylammonium trifluoroacetate were synthesized from tetra-*n*-butylammonium hydroxide and the corresponding carboxylic acids (all from Fluka) following routine approaches.[71,81]

(*R*)-(+)-2-(*tert*-Butyldiphenylsilyloxymethyl)oxirane **1**, (*R*)-(+)-2-(triisopropylsilyloxymethyl)oxirane **2**, (*S*)-(+)-2-(*tert*-butyldimethylsilyloxymethyl)oxirane **3**, (*rac*)-(±)-2-(*tert*-butyldimethylsilyloxymethyl)oxirane **4**, (*S*)-(+)-2-(oleoyloxymethyl)oxirane **5**, and (*rac*)-(±)-2-(oleoyloxymethyl)oxirane **6** were prepared from chiral or racemic glycidols (all from Fluka) analogously to conventional methods[66] or as described elsewhere.[80] No attempts were made to optimize these particular procedures that afforded starting substrates **1–6** with spectral and physicochemical parameters comparable to those reported in the literature.[66,80,82]

The detailed account of analytical criteria proposed for assessing regiochemistry of the prepared compounds by ^1H and ^{13}C NMR spectroscopy is given in ESI (Section 5: Table S2). For full ^1H and ^{13}C NMR spectral characteristics of the compounds synthesized, see ESI (Section 6).

3.2. General procedure for one-pot, two-step conversion of glycidyl derivatives (1–6) into halohydrins I (7–11, 61), halohydrins II (12–14), and halohydrins III (15–19)

A solution of glycidyl substrate **1–6** (1.00 mmol) and tetra-*n*-butylammonium halide (3.00 mmol) in alcohol-free chloroform (10.0 mL) at room temperature was treated under argon with trifluoroacetic acid (0.115 mL, 1.50 mmol) for 5 min–1 h. Then, the corresponding either acyl chloride (1.50 mmol) or silyl chloride (3.00 mmol) and, after *ca.* 5 min, 4-*N*,*N*-dimethylaminopyridine (0.733 g, 6.00 mmol) [or pyridine (1.61 mL, 20.0 mmol) used in the case of acylation only] were added successively and the reaction mixture was left at room temperature for 5 min–24 h. The solution was passed through a chloroform-filled silica gel pad (~5 g), which was washed with the same solvent (~100 mL). Chloroform was removed under reduced pressure and the fully-protected C3-synthons **7–19**, **61** were isolated in pure state (>99%, ^1H NMR spectroscopy) by flash column silica gel chromatography (eluent for **7**, **9**, **10**: toluene–pentane = 80 : 20, v/v; eluent for **8**, **11**: toluene–EtOAc = 98 : 2, v/v; eluent for **12–14**: pentane–toluene = 80 : 20, v/v; eluent for **15**: toluene–pentane = 50 : 50, v/v; eluent for **16-19**, **61**: toluene).

1-Iodo-2-acetyl-3-*O*-triisopropylsilyl-*sn*-glycerol 8. Obtained from (*R*)-(+)-2-(triisopropylsilyloxymethyl)oxirane (**2**; 0.230 g, 1.00 mmol) using Bu_4NI (1.108 g, 3.00 mmol), acetyl chloride (0.107 mL, 1.50 mmol) and pyridine (reaction times, stage I: 5 min; stage II: 1.5 h). Yield: 0.380 g (95%, colorless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.73; $[\alpha]_D^{20} = +9.82$ (*c* 11.19,

$CHCl_3$); Found: C, 40.96; H, 7.33; I, 31.75%. $C_{14}H_{29}IO_3Si$ (400.37) requires C, 42.00; H, 7.30; I, 31.70%.

1-Iodo-2-oleoyl-3-*O*-triisopropylsilyl-*sn*-glycerol 9. Obtained from (*R*)-(+)-2-(triisopropylsilyloxymethyl)oxirane (**2**; 0.230 g, 1.00 mmol) using Bu_4NI (1.108 g, 3.00 mmol), oleoyl chloride (0.496 mL, 1.50 mmol) and pyridine (reaction times, stage I: 5 min; stage II: 2 h). Yield: 0.579 g (93%, colorless oil); R_f (toluene–pentane = 80 : 20, v/v) = 0.88; $[\alpha]_D^{20}$ = +5.77 (*c* 10.15, $CHCl_3$); Found: C, 57.93; H, 9.51; I, 20.41%. $C_{30}H_{59}IO_3Si$ (622.78) requires C, 57.86; H, 9.55; I, 20.38%.

1-*O*-*tert*-Butyldimethylsilyl-2-oleoyl-3-iodo-*sn*-glycerol 10. Obtained from (*S*)-(+)-2-(*tert*-butyldimethylsilyloxymethyl)-oxirane (**3**; 0.188 g, 1.00 mmol) using Bu_4NI (1.108 g, 3.00 mmol), oleoyl chloride (0.496 mL, 1.50 mmol) and 4-DMAP (reaction times, stage I: 5 min; stage II: 10 min). Yield: 0.545 g (94%, colorless oil); R_f (toluene–pentane = 80 : 20, v/v) = 0.73; $[\alpha]_D^{20}$ = −3.21 (*c* 7.88, $CHCl_3$); Found: C, 55.93; H, 9.17; I, 21.90%. $C_{27}H_{53}IO_3Si$ (580.70) requires C, 55.84; H, 9.20; I, 21.85%.

1-*O*-*tert*-Butyldimethylsilyl-2-*O*-triisopropylsilyl-3-iodo-*sn*-glycerol 13. Obtained from (*S*)-(+)-2-(*tert*-butyldimethylsilyloxymethyl)oxirane (**3**; 0.188 g, 1.00 mmol) using Bu_4NI (1.108 g, 3.00 mmol), TIPSCl (0.636 mL, 3.00 mmol) and 4-DMAP (reaction times, stage I: 5 min; stage II: 24 h). Yield: 0.434 g (92%, colorless oil); R_f (pentane) = 0.29; $[\alpha]_D^{20}$ = +1.44 (*c* 10.34, $CHCl_3$); Found: C, 45.83; H, 8.70; I, 26.90%. $C_{18}H_{41}IO_2Si_2$ (472.59) requires C, 45.75; H, 8.74; I, 26.85%.

1-Oleoyl-2-*O*-*tert*-butyldimethylsilyl-3-iodo-*sn*-glycerol 15. Obtained from (*S*)-(+)-2-(oleoyloxymethyl)oxirane (**5**; 0.338 g, 1.00 mmol) using Bu_4NI (1.108 g, 3.00 mmol), TBDMSCl (0.452 g, 3.00 mmol) and 4-DMAP (reaction times, stage I: 5 min; stage II: 1.5 h). Yield: 0.552 g (95%, colorless oil); R_f (pentane–toluene = 80 : 20, v/v) = 0.71; $[\alpha]_D^{20}$ = +6.44 (*c* 12.79, $CHCl_3$); Found: C, 55.77; H, 9.22; I, 21.81%. $C_{27}H_{53}IO_3Si$ (580.70) requires C, 55.84; H, 9.20; I, 21.85%.

1-Oleoyl-2-*O*-triethylsilyl-3-iodo-*sn*-glycerol 16. Obtained from (*S*)-(+)-2-(oleoyloxymethyl)oxirane (**5**; 0.338 g, 1.00 mmol) using Bu_4NI (1.108 g, 3.00 mmol), triethylsilyl chloride (0.316 mL, 3.00 mmol) and 4-DMAP (reaction times, stage I: 5 min; stage II: 5 min). Yield: 0.540 g (93%, colorless oil); R_f (pentane–toluene–EtOAc, 40 : 50 : 10, v/v/v) = 0.89; $[\alpha]_D^{20}$ = +4.94 (*c* 10.58, $CHCl_3$); Found: C, 55.90; H, 9.17; I, 21.89%. $C_{27}H_{53}IO_3Si$ (580.70) requires C, 55.84; H, 9.20; I, 21.85%.

1-Oleoyl-2-palmitoyl-3-iodo-*sn*-glycerol 61. Obtained from (*S*)-(+)-2-(oleoyloxymethyl)oxirane (**5**; 0.338 g, 1.00 mmol) using Bu_4NI (1.108 g, 3.00 mmol), palmitoyl chloride (0.453 mL, 1.50 mmol) and 4-DMAP (reaction times, stage I: 5 min; stage II: 10 min). Yield: 0.683 g (97%, colorless oil); R_f (pentane–toluene–EtOAc, 40 : 50 : 10, v/v/v) = 0.80; $[\alpha]_D^{20}$ = +3.56 (*c* 12.63, $CHCl_3$); lit.[68] (for 1-iodo-2-palmitoyl-3-oleoyl-*sn*-glycerol) $[\alpha]_D^{20}$ = -3.62 (*c* 10.28, $CHCl_3$); Found: C, 62.95; H, 9.90; I, 18.10%. $C_{37}H_{69}IO_4$ (704.85) requires C, 63.05; H, 9.87; I, 18.00%.

3.3. Typical procedure for the transformation of halohydrins I (8–10), halohydrin II (13) and halohydrin III (15) to terminal *O*-acylates (20, 21, 26, 27, 47–49, 54)

To a solution of the requisite iodohydrin **8–10**, **13** or **15** (1.00 mmol) in anhydrous toluene (7.0 mL) was added the corresponding tetra-*n*-butylammonium carboxylate (3.00 mmol) and the reaction system was stirred under argon in a pressure-proof glass ampoule at 80 °C (bath) for 1.5 h. The solution was passed through a short silica gel pad (~5 g), the support was washed with chloroform (~150 mL) and the solvents were evaporated *in vacuum*. The target esters **20**, **21**, **26**, **27**, **47–49** were isolated in pure state (>99%, ^{1}H NMR spectroscopy) by flash column silica gel chromatography (mobile phase for **20**, **21**, **47–49**: toluene–EtOAc, 98 : 2, v/v; mobile phase for **26**: toluene; mobile phase for **27**: pentane–toluene: 50 : 50, v/v).

Using silver trifluoroacetate (3.00 mmol) instead, the trifluoroacetyl ester **54** of 1-oleoyl-2-*O*-*tert*-butyldimethylsilyl-3-iodo-*sn*-glycerol **15** was obtained in a similar way as described below.

1-Oleoyl-2-acetyl-3-*O*-triisopropylsilyl-*sn*-glycerol 20. Prepared from 1-iodo-2-acetyl-3-*O*-triisopropylsilyl-*sn*-glycerol (**8**; 0.400 g, 1.00 mmol) and tetra-*n*-butylammonium oleate (1.57 g, 3.00 mmol). Yield: 0.511 g (92%, colorless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.60; $[\alpha]_D^{20}$ = +13.45 (*c* 3.67, $CHCl_3$); lit.[29] $[\alpha]_D^{20}$ = +11.28 (*c* 9.87, $CHCl_3$); Found: C, 69.31; H, 11.24%. $C_{32}H_{62}O_5Si$ (554.92) requires C, 69.26; H, 11.26%.

1-Acetyl-2-oleoyl-3-*O*-triisopropylsilyl-*sn*-glycerol 21. Acquired by treatment of 1-iodo-2-oleoyl-3-*O*-triisopropylsilyl-*sn*-glycerol (**9**; 0.623 g, 1.00 mmol) with tetra-*n*-butylammonium acetate (0.90 g, 3.00 mmol). Yield: 0.508 g (92%, colorless oil); R_f (pentane–toluene–EtOAc, 40 : 50 : 10, v/v/v) = 0.58; $[\alpha]_D^{20}$ = +15.72 (*c* 11.38, $CHCl_3$); Found: C, 69.22; H, 11.30%. $C_{32}H_{62}O_5Si$ (554.92) requires C, 69.26; H, 11.26%.

1-*O*-*tert*-Butyldimethylsilyl-2-*O*-triisopropylsilyl-3-acetyl-*sn*-glycerol 26. Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-iodo-*sn*-glycerol (**13**; 0.473 g, 1.00 mmol) and tetra-*n*-butylammonium acetate (0.90 g, 3.00 mmol). Yield: 0.384 g (95%, colorless oil); R_f (toluene) = 0.40; $[\alpha]_D^{20}$ = −25.51 (*c* 10.11, $CHCl_3$); Found: C, 59.59; H, 10.83%. $C_{20}H_{44}O_4Si_2$ (404.73) requires C, 59.35; H, 10.96%.

1-*O*-*tert*-Butyldimethylsilyl-2-*O*-triisopropylsilyl-3-oleoyl-*sn*-glycerol 27. Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-iodo-*sn*-glycerol (**13**; 0.473 g, 1.00 mmol) and tetra-*n*-butylammonium oleate (1.57 g, 3.00 mmol). Yield: 0.583 g (93%, colorless oil); R_f (pentane–toluene: 50 : 50, v/v) = 0.61; $[\alpha]_D^{20}$ = −15.65 (*c* 9.06, $CHCl_3$); Found: C, 69.15; H, 11.79%. $C_{36}H_{74}O_4Si_2$ (627.14) requires C, 68.94; H, 11.89%.

1-*O*-*tert*-Butyldimethylsilyl-2-oleoyl-3-acetyl-*sn*-glycerol 47. Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-oleoyl-3-iodo-*sn*-glycerol (**10**; 0.581 g, 1.00 mmol) and tetra-*n*-butylammonium acetate (0.90 g, 3.00 mmol). Yield: 0.482 g (94%, colorless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.58; $[\alpha]_D^{20}$ = −12.60 (*c* 8.21, $CHCl_3$); Found: C, 67.69; H, 11.06%. $C_{29}H_{56}O_5Si$ (512.85) requires C, 67.92; H, 11.01%.

1-*O*-*tert*-Butyldimethylsilyl-2-oleoyl-3-palmitoyl-*sn*-glycerol 48. Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-oleoyl-3-iodo-*sn*-glycerol (**10**; 0.581 g, 1.00 mmol) and tetra-*n*-butylammonium palmitate (1.49 g, 3.00 mmol). Yield: 0.652 g (92%, colorless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.68; $[\alpha]_D^{20}$ = –7.03 (*c* 3.08, $CHCl_3$); Found: C, 72.95; H, 11.87%. $C_{43}H_{84}O_5Si$ (709.22) requires C, 72.82; H, 11.94%.

1-Oleoyl-2-*O*-*tert*-butyldimethylsilyl-3-trifluoroacetyl-*rac*-glycerol 54. To a solution of 1-oleoyl-2-*O*-*tert*-butyldimethylsilyl-3-iodo-*sn*-glycerol (**15**; 0.581 g, 1.00 mmol) in anhydrous toluene (6.0 mL) was added silver trifluoroacetate (0.663 g, 3.00 mmol) and the reaction mixture was stirred under argon at 60 °C for 2 h in a tightly stoppered glass ampoule. The solution was passed through a silica gel pad (~5 g) prepared in the same solvent. The support was washed with toluene (~150 mL) and fractions containing the target product were combined. Evaporation of the solvent under reduced pressure gave the title compound **54** (0.538 g, 95%) as a colorless oil. R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.80; $[\alpha]_D^{20}$ = 0.00 (*c* 8.39, $CHCl_3$); Found: C, 61.02; H, 9.49%. $C_{29}H_{53}F_3O_5Si$ (566.81) requires C, 61.45; H, 9.43%.

3.4. Typical procedure for the direct conversion of silyl ethers (20, 21, 28, 29, and 56) into trichloroacetates (22, 23, 30, 31, and 57)

A mixture of the starting silyl ether **20**, **21**, **28**, **29** or **56** (1.00 mmol), neat trichloroacetic anhydride (9.00–12.00 mmol) and triethylamine tris(hydrofluoride) (2.00–3.00 mmol) was kept under argon, in a pressure-proof glass ampoule at 80 °C (bath) for 2–6 h. The system was taken in toluene–EtOAc (98 : 2, v/v; 5 mL) and the trichloroacetyl derivatives **22**, **23**, **30**, **31**, and **57** were isolated in pure state (>99%, ^{1}H NMR spectroscopy) by flash column silica gel chromatography (mobile phase: toluene–EtOAc = 98 : 2, v/v).

1-Oleoyl-2-acetyl-3-trichloroacetyl-*sn*-glycerol 22. Obtained from 1-oleoyl-2-acetyl-3-*O*-triisopropylsilyl-*sn*-glycerol (**20**; 0.555 g, 1.00 mmol), trichloroacetic anhydride (1.644 mL, 9.00 mmol) and triethylamine tris(hydrofluoride) (0.326 mL, 2.00 mmol) for 2 h. Yield: 0.500 g (92%, colorless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.58; $[\alpha]_D^{20}$ = –0.41 (*c* 5.17, $CHCl_3$); lit.[29] $[\alpha]_D^{20}$ = –0.40 (*c* 7.18, $CHCl_3$); Found: C, 55.29; H, 7.52; Cl, 19.70%. $C_{25}H_{41}Cl_3O_6$ (543.95) requires C, 55.20; H, 7.60; Cl, 19.55%.

1-Acetyl-2-oleoyl-3-trichloroacetyl-*sn*-glycerol 23. Obtained from 1-acetyl-2-oleoyl-3-*O*-triisopropylsilyl-*sn*-glycerol (**21**; 0.555 g, 1.00 mmol), trichloroacetic anhydride (1.644 mL, 9.00 mmol) and triethylamine tris(hydrofluoride) (0.326 mL, 2.00 mmol) for 2 h. Yield: 0.490 g (90%, colorless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.51; $[\alpha]_D^{20}$ = +1.78 (*c* 10.31, $CHCl_3$); Found: C, 55.25; H, 7.56; Cl, 19.60%. $C_{25}H_{41}Cl_3O_6$ (543.95) requires C, 55.20; H, 7.60; Cl, 19.55%.

1-Oleoyl-2-trichloroacetyl-3-acetyl-*sn*-glycerol 30. Obtained from 1-oleoyl-2-*O*-triisopropylsilyl-3-acetyl-*sn*-glycerol (**28**; 0.555 g, 1.00 mmol), trichloroacetic anhydride (2.192 mL, 12.00 mmol) and triethylamine tris(hydrofluoride) (0.488 mL, 3.00 mmol) for 6 h. Yield: 0.495 g (91%, colorless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.50; $[\alpha]_D^{20}$ = –0.69 (*c* 9.15, $CHCl_3$); lit.[29] $[\alpha]_D^{20}$ = –0.68 (*c* 9.77, $CHCl_3$); Found: C, 55.27; H, 7.60; Cl, 19.57%. $C_{25}H_{41}Cl_3O_6$ (543.95) requires C, 55.20; H, 7.60; Cl, 19.55%.

1-Acetyl-2-trichloroacetyl-3-oleoyl-*sn*-glycerol 31. Obtained from 1-acetyl-2-*O*-triisopropylsilyl-3-oleoyl-*sn*-glycerol (**29**; 0.555 g, 1.00 mmol), trichloroacetic anhydride (2.192 mL, 12.00 mmol) and triethylamine tris(hydrofluoride) (0.488 mL, 3.00 mmol) for 6 h. Yield: 0.506 g (93%, colorless oil); $[\alpha]_D^{20}$ = +0.66 (*c* 8.33, $CHCl_3$); all other physicochemical and spectral characteristics were identical with those of the previous product.

1-Oleoyl-2-trichloroacetyl-3-acetyl-*rac*-glycerol 57. Obtained from 1-oleoyl-2-*O*-*tert*-butyldimethylsilyl-3-acetyl-*rac*-glycerol (**56**; 0.513 g, 1.00 mmol), trichloroacetic anhydride (2.192 mL, 12.00 mmol) and triethylamine tris(hydrofluoride) (0.488 mL, 3.00 mmol) for 2.5 h. Yield: 0.504 g (93%, colorless oil); excluding the lack of optical activity, all other physicochemical and spectral characteristics were identical with those of compounds **30** and **31**.

3.5. Typical procedure for the direct functionalization of silyl ethers (26, 27, 47–49, 11, and 16) to fatty acid esters (28, 29, 50–53, 60, and 61)

To a solution of the silyl ether **26**, **27**, **47–49**, **11** or **16** (1.00 mmol) and tetra-*n*-butylammonium bromide (Bu_4NBr; 0.645 g, 2.00 mmol) [or tetra-*n*-butylammonium iodide (Bu_4NI; 0.739 g, 2.00 mmol)] in alcohol-free chloroform (3.0 mL), a mixture of the appropriate carboxylic acid anhydride (3.00 mmol) and trimethylbromosilane (TMSBr; 0.195 mL, 1.50 mmol) [or trimethyliodosilane (TMSI; 0.204 mL, 1.50 mmol)] 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–7 h. Chloroform was removed under reduced pressure and the residue was subjected to flash column silica gel chromatography (mobile phase: toluene–EtOAc = 98 : 2, v/v) to give the expected acylates **28**, **29**, **50–53**, **60**, and **61** (purity >99%, ^{1}H NMR spectroscopy).

1-Oleoyl-2-*O*-triisopropylsilyl-3-acetyl-*sn*-glycerol 28. Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-acetyl-*sn*-glycerol (**26**; 0.405 g, 1.00 mmol), oleic anhydride (1.641 g, 3.00 mmol), Bu_4NBr, and TMSBr for 2 h. Yield: 0.510 g (92%, colorless oil); R_f (pentane–toluene–EtOAc: 40 : 50 : 10, v/v/v) = 0.56; $[\alpha]_D^{20}$ = -1.20 (*c* 18.05, $CHCl_3$); Found: C, 69.05; H, 11.30%. $C_{32}H_{62}O_5Si$ (554.92) requires C, 69.26; H, 11.26%.

1-Acetyl-2-*O*-triisopropylsilyl-3-oleoyl-*sn*-glycerol 29. Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-oleoyl-*sn*-glycerol (**27**; 0.627 g, 1.00 mmol), acetic anhydride (0.284 mL, 3.00 mmol), Bu_4NBr, and TMSBr for 2 h. Yield: 0.527 g (95%, colorless oil); $[\alpha]_D^{20}$ = +1.14 (*c* 17.03, $CHCl_3$); all other physicochemical and spectral characteristics were identical with those of the previous product.

1-Palmitoyl-2-oleoyl-3-acetyl-*sn*-glycerol 50. Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-oleoyl-3-acetyl-*sn*-glycerol (**47**; 0.513 g, 1.00 mmol), palmitic anhydride (1.484 g, 3.00 mmol), Bu_4NBr, and TMSBr for 2 h. Yield: 0.592 g (93%, colorless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.54; $[\alpha]_D^{20}$ = –0.74 (*c* 4.13, $CHCl_3$); Found: C, 73.50; H, 11.43%. $C_{39}H_{72}O_6$ (636.98) requires C, 73.54; H, 11.39%.

1-Acetyl-2-oleoyl-3-palmitoyl-*sn*-glycerol 51. Prepared from 1-*O*-*tert*-butyldimethylsilyl-2-oleoyl-3-palmitoyl-*sn*-glycerol (**48**; 0.709 g, 1.00 mmol), acetic anhydride (0.284 mL, 3.00 mmol), Bu_4NBr, and TMSBr for 2 h. Yield: 0.574 g (90%, colorless oil); $[\alpha]_D^{20} = +0.76$ (*c* 3.12, CHCl3); lit.[29] $[\alpha]_D^{20} = +0.72$ (*c* 11.73, $CHCl_3$); all other physicochemical and spectral characteristics were identical with those of **50**.

1-Oleoyl-2-acetyl-3-iodo-*rac*-glycerol 60. Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-acetyl-3-iodo-*rac*-glycerol (**11**; 0.358 g, 1.00 mmol), oleic anhydride (1.641 g, 3.00 mmol), Bu_4NI, and TMSI for 2 h. Yield: 0.467 g (92%, colorless oil); R_f (pentane–toluene–EtOAc, 40 : 50 : 10, v/v/v) = 0.67; Found: C, 54.43; H, 8.11; I, 24.80%. $C_{23}H_{41}IO_4$ (508.47) requires C, 54.33; H, 8.13; I, 24.96%.

3.6. Typical procedure for the direct transformation of silyl ethers (26, 27) into trifluoroacetates (34, 35) [Scheme 5: step (i)]

To a solution of silyl ether **26** or **27** (1.00 mmol) and trifluoroacetic anhydride (1.67 mL, 12.00 mmol) in chloroform (3.0 mL), methanol (0.122 mL, 3.0 mmol) was added and the reaction system was kept under argon in a pressure-proof glass ampoule at 70 °C (bath) for 2 h. Solvents were evaporated under reduced pressure to give the target compounds **34** and **35** (purity: >99%, ^{1}H NMR spectroscopy) in a straightforward manner.

1-Trifluoroacetyl-2-*O*-triisopropylsilyl-3-acetyl-*sn*-glycerol 34

Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-acetyl-*sn*-glycerol (**26**; 0.405 g, 1.00 mmol). Yield: 0.386 g (100%, pale yellowish oil); R_f (toluene–EtOAc, 98 : 2, v/v) = 0.39; $[\alpha]_D^{20} = +11.77$ (*c* 14.82, $CHCl_3$); Found: C, 49.83; H, 7.53%. $C_{16}H_{29}F_3O_5Si$ (386.48) requires C, 49.72; H, 7.56%.

1-Trifluoroacetyl-2-*O*-triisopropylsilyl-3-oleoyl-*sn*-glycerol 35. Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-oleoyl-*sn*-glycerol (**27**; 0.627 g, 1.00 mmol). Yield: 0.608 g (100%, pale yellowish oil); R_f (pentane–toluene: 50 : 50, v/v) = 0.55; $[\alpha]_D^{20} = +9.12$ (*c* 15.73, $CHCl_3$); Found: C, 63.24; H, 9.70%. $C_{32}H_{59}F_3O_5Si$ (608.89) requires C, 63.12; H, 9.77%.

3.7. Typical procedure for removal of trichloroacetyl- (22, 23, 30, 31, and 57) and trifluoroacetyl groups (34, 35 and 54) to produce alcohols (24, 25, 32, 33, 36–38, 55, and 58)

To a solution of either trichloroacetyl- **22**, **23**, **30**, **31**, or **57** (0.544 g, 1.00 mmol) or trifluoroacetyl derivative **34**, **35** or **54** (1.00 mmol) in tetrahydrofuran (5.0 mL), a mixture of pyridine (4.0 mL, 50 mmol) and methanol (20.3 mL, 500 mmol) was added and the reaction system was left at room temperature for 30 min–2 h. 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 the deprotected compounds **24**, **25**, **32**, **33**, **36-38**, **55**, and **58** directly (purity >99%, ^{1}H NMR spectroscopy).

2-*O*-Triisopropylsilyl-3-iodo-*sn*-glycerol **38** was obtained in a similar way by following the one-pot, two-step procedure described bellow.

1-Oleoyl-2-acetyl-*sn*-glycerol 24. Produced from 1-oleoyl-2-acetyl-3-trichloroacetyl-*sn*-glycerol (**22**) for 2 h. Yield: 0.397 g (100%, colorless oil); R_f (toluene–EtOAc = 80 : 20, v/v) = 0.26; $[\alpha]_D^{20} = -5.47$ (c, 4.82, $CHCl_3$); lit.[29] $[\alpha]_D^{20} = -5.42$ (c, 5.07, $CHCl_3$); Found: C, 69.38; H, 10.58%. $C_{23}H_{42}O_5$ (398.58) requires C, 69.31; H, 10.62%.

1-Acetyl-2-oleoyl-*sn*-glycerol 25. Obtained from 1-acetyl-2-oleoyl-3-trichloroacetyl-*sn*-glycerol (**23**) for 2 h. Yield: 0.399 g (100%, colorless oil); R_f (toluene–EtOAc = 80 : 20, v/v) = 0.27; $[\alpha]_D^{20} = -1.62$ (*c* 6.53, $CHCl_3$); Found: C, 69.51; H, 10.62%. $C_{23}H_{42}O_5$ (398.58) requires C, 69.31; H, 10.62%.

1-Oleoyl-3-acetyl-*sn*-glycerol 32. Obtained from 1-oleoyl-2-trichloroacetyl-3-acetyl-*sn*-glycerol (**30**) for 2 h. Yield: 0.397 g (100%, colorless oil); R_f (toluene–EtOAc = 80 : 20, v/v) = 0.32; $[\alpha]_D^{20} = -0.27$ (*c* 10.85, $CHCl_3$); lit.[29] $[\alpha]_D^{20} = -0.28$ (*c* 9.15, $CHCl_3$); Found: C, 69.25; H, 10.70%. $C_{23}H_{42}O_5$ (398.58) requires C, 69.31; H, 10.62%.

1-Acetyl-3-oleoyl-*sn*-glycerol 33. Obtained from 1-acetyl-2-trichloroacetyl-3-oleoyl-*sn*-glycerol (**31**) for 2 h. Yield: 0.399 g (100%, colorless oil); $[\alpha]_D^{20} = +0.28$ (*c* 9.05, $CHCl_3$); all other physicochemical and spectral characteristics were identical with those of **32**.

2-*O*-Triisopropylsilyl-3-oleoyl-*sn*-glycerol 37. Prepared from 1-trifluoroacetyl-2-*O*-triisopropylsilyl-3-oleoyl-*sn*-glycerol (**35**; 0.609 g, 1.00 mmol) for 30 min. Yield: 0.511 g (100%, colorless oil); R_f (pentane–toluene–EtOAc, 40 : 50 : 10, v/v/v) = 0.44; $[\alpha]_D^{20} = +9.01$ (*c* 10.05, $CHCl_3$); Found: C, 70.48; H, 11.60%. $C_{30}H_{60}O_4Si$ (512.88) requires C, 70.25; H, 11.79%.

2-*O*-Triisopropylsilyl-3-iodo-*sn*-glycerol 38. To a solution of 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-iodo-*sn*-glycerol (**13**; 0.473 g, 1.00 mmol) in chloroform (3.0 mL) were consecutively added trifluoroacetic anhydride (1.67 mL, 12.00 mmol) and methanol (0.122 mL, 3.0 mmol), and the reaction system was heated at 70 °C for 2 h (pressure tube). The solvents were distilled off, the residue was taken in tetrahydrofuran (5.0 mL) and the solution was treated at room temperature for 30 min with a mixture of pyridine (4.0 mL, 50 mmol) and methanol (20.3 mL, 500 mmol). Evaporation of the solvents under reduced pressure afforded the title compound **38**. Yield: 0.357 g (100%, pale yellowish oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.55; $[\alpha]_D^{20} = +11.25$ (*c* 8.81, $CHCl_3$); Found: C, 40.30; H, 7.51; I, 35.50%. $C_{12}H_{27}IO_2Si$ (358.33) requires C, 40.22; H, 7.59; I, 35.41%.

3.8. Typical procedure for one-pot conversion of trichloroacetyl- (22, 23, 30, 31, and 57) and trifluoroacetyl derivatives (54) into the corresponding fatty acid esters (39–46, 56 and 59)

First stage. A solution of **22**, **23**, **30**, **31**, **54** or **57** (1.00 mmol) in tetrahydrofuran (5.0 mL) was treated at room temperature with a mixture of pyridine (4.0 mL, 50 mmol) and methanol (20.3 mL, 500 mmol) for 30 min–2 h, and the volatile materials were removed under reduced pressure.

Second stage. The residue containing the deprotected alcohol species was dissolved in alcohol-free chloroform (10.0 mL) containing pyridine (1.61 mL, 20.0 mmol), and the mixture was reacted at −20 °C with a solution of a requisite acyl chloride (2.00 mmol) in alcohol-free chloroform (10.0 mL). After keeping the reaction system at room temperature for 2–3.5 h, the solution

was passed through a chloroform-filled silica gel pad (~5 g), which was washed with the same solvent (~100 mL). Chloroform was removed under reduced pressure and the thus acylated products **41–46**, **56** were isolated in pure state (>99%, ^{1}H NMR spectroscopy) by flash column silica gel chromatography (mobile phase: toluene–EtOAc = 98 : 2, v/v).

1-Acetyl- (**39**) and 1-oleoyl-2-*O*-triisopropylsilyl-3-iodo-*sn*-glycerol (**40**) were synthesized analogously by a three-step, one-pot derivatization of 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-iodo-*sn*-glycerol (**13**) (see below).

The Mosher ester (**59**) of 1,3-diglyceride (**58**) was acquired from C2-trichloroacetate (**57**) in a slightly modified manner concerning the purification process only.

1-Oleoyl-2-*O*-triisopropylsilyl-3-iodo-*sn*-glycerol 40. Synthesized in a one-pot, three-step procedure from 1-*O*-*tert*-butyldimethylsilyl-2-*O*-triisopropylsilyl-3-iodo-*sn*-glycerol (**13**; 0.473 g, 1.00 mmol) and oleoyl chloride (0.66 mL, 2.00 mmol) (stage III: r.t./2 h), as described for **39**. Subsequent flash column silica gel chromatography (mobile phase: pentane–toluene = 50 : 50, v/v) gave the title compound **40** (purity >99%, ^{1}H NMR spectroscopy). Yield: 0.585 g (94%, colorless oil); R_f (pentane–toluene = 50 : 50, v/v) = 0.69; $[\alpha]_D^{20}$ = +8.12 (*c* 6.03, $CHCl_3$); Found: C, 58.01; H, 9.42; I, 20.45%. $C_{30}H_{59}IO_3Si$ (622.78) requires C, 57.86; H, 9.55; I, 20.38%.

1-Oleoyl-2-[*R*-(−)-α-methoxy-α-trifluoromethylphenylacetyl]-3-acetyl-*rac*-glycerol 59. Acquired according to the typical procedure from 1-oleoyl-2-trichloroacetyl-3-acetyl-*rac*-glycerol (**57**; 0.544 g, 1.00 mmol) *via* **58** and *R*-(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride (0.374 mL, 2.00 mmol) (stage I; 2 h; stage II: 20 h) with the exception that after removing the solvents, the residue was taken in toluene–EtOAc (98 : 2, v/v, 5 mL) and the solution was passed through a silica gel pad (~5 g) prepared in the same solvent system. The support was washed with this eluent (50 mL), fractions containing the product were combined and the solution was concentrated under reduced pressure to afford the crude Mosher ester **59**, which was examined next by ^{1}H and ^{13}C NMR without supplementary purification. Yield calcd for $C_{33}H_{49}F_3O_7$ (614.73): 0.565 g (92%, colorless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.47.

3.9. Typical procedure for transformation of terminal C3-iodohydrins (60, 61) into quaternary pyridinium salts (62, 63)

A mixture of iodoglyceride **60** or **61** (1.00 mmol) and pyridine (2.4 mL, 30 mmol) was heated in a pressure glass ampoule under argon at 80 °C for 18 h. The excess pyridine was removed under reduced pressure and the residue was subjected to flash column silica gel chromatography using CH_2Cl_2–MeOH–H_2O (65 : 25 : 4, v/v/v) as the mobile phase. The thus isolated products were additionally recrystallized with dry diethyl ether (−20 °C) to give the target compounds **62** and **63** (purity >99%, ^{1}H NMR spectroscopy).

(±)-*N*-(1-Oleoyl-2-acetyl-3-propyl)pyridinium iodide 62. Obtained from 1-oleoyl-2-acetyl-3-iodo-*rac*-glycerol (**60**; 0.508 g, 1.00 mmol). Yield: 0.528 g (90%, amorphous yellowish solid); R_f (CH_2Cl_2–MeOH–H_2O, 65 : 25 : 4, v/v/v) = 0.69; Found: C, 57.31; H, 7.81; N, 2.40%. $C_{28}H_{46}INO_4$ (587.58) requires C, 57.24; H, 7.89; N, 2.38%.

(−)-*N*-(1-Oleoyl-2-palmitoyl-3-propyl)pyridinium iodide 63. Acquired from 1-oleoyl-2-palmitoyl-3-iodo-*sn*-glycerol (**61**; 0.705 g, 1.0 mmol). Yield: 0.682 g (87%, yellowish solid); mp: 83.6–85.0 °C (from diethyl ether); R_f (CH_2Cl_2–MeOH–H_2O, 65 : 25 : 4, v/v/v) = 0.74; $[\alpha]_D^{20}$ = −16.26 (*c* 3.26, $CHCl_3$); Found: C, 64.44; H, 9.48; N, 1.81%. $C_{42}H_{74}INO_4$ (783.95) requires C, 64.35; H, 9.51; N, 1.79%.

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