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Stereospecific and regioselective opening of an oxirane system. A new efficient entry to 1- or 3-monoacyl- and 1- or 3-monoalkyl-*sn*-glycerols

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Abstract—Acyl or alkyl glycidols in the presence of trifluoroacetic anhydride (TFAA) and trifluoroacetate anions, undergo a regioselective and stereospecific opening of the oxirane system to produce the bis(trifluoroacetylated) derivatives, from which the corresponding 1(3)-monoacyl-*sn*-glycerols or 1(3)-monoalkyl-*sn*-glycerols can be obtained directly in high purity (>99%) and in quantitative yields.

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1. Introduction

The importance of stereochemically pure 1(3)-monoacyl-*sn*-glycerols (MAG) and their 1(3)-monoalkyl-*sn*-analogues (MALKG) as physiological effectors per se[1] or as chiral building blocks in the asymmetric synthesis of various bioactive lipids[2] and agents for biochemical[3] or medicinal[4] intervention, has been well documented.

Despite the apparent structural simplicity, access to the aforementioned classes of lipid mediators is rather limited as the presence of two adjacent hydroxyl functions makes 1(3)-monoacyl-*sn*-glycerols highly susceptible to acyl migration.[5] This process, which is promoted by acids, bases or heat, not only results in loss of chirality at C-2, but also poses severe problems in isolation and storage of these compounds. For derivatives bearing polyunsaturated systems (e.g., oleoyl or arachidonoyl moieties), a high propensity to autooxidation and decomposition in the presence of even mild Lewis acids (e.g., $BF_3{\cdot}OEt_2$)[6] further limits the number of suitable synthetic procedures.

These problems are most acute in the classical synthesis of 1(3)-MAG[7] or 1(3)-MALKG[8] where 1,2(2,3)-isopropylidene-*sn*-glycerol derivatives are commonly used as starting materials. The prolonged treatment with concentrated mineral acids at elevated temperature (conditions that are typically required for acetal cleavage in these approaches), adversely affects the purity of the isolated 1(3)-MAG due to extensive side-product formation (e.g., acyl migration, formation of cyclic systems, racemization, etc.).[7] Although various reagent systems, for example, dimethylboronbromide[9] or trifluoroacetic acid with triethyl borate-2,2,2-trifluoroethanol (8:1 v/v)[10] have been advocated as superior to mineral acids for the removal of the isopropylidene group, these procedures require painstaking chromatography, which often has a detrimental effect on the stereochemical purity of compounds isolated.[11]

To overcome complications inherent in most protocols involving protection/deprotection steps, two procedures based on a titanium(IV) isopropoxide-promoted acidolysis/or phenolysis of optically active glycidols were proposed for accessing unprotected 1(3)-monoacyl-[12]/or 1(3)-monoaryl-*sn*-glycerols[13] in one-pot reactions. In the most recent modification, involving a synthesis of

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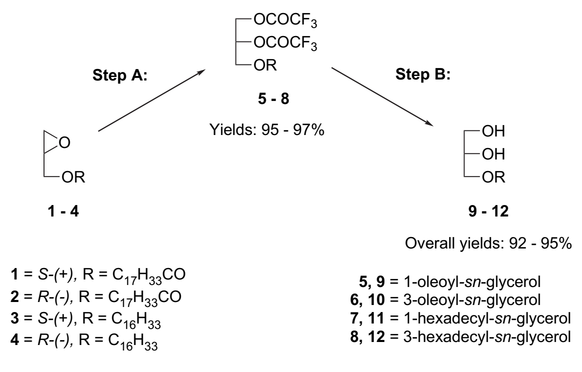
1(3)-hexadecyl-*sn*-glycerol,[14] a *tert*-butydiphenylsilyl (TBDPS) ether derivative of a chiral glycidol was used as a substrate and, after opening the oxirane system with 1-hexadecanol using boron trifluoride etherate as catalyst, the TBDPS group was removed by means of tetrabutylammonium fluoride. Unfortunately, in comparison with approaches based on 1,2-isopropylideneglycerol derivatives, these methods although simple, are rather inefficient and provide the target compounds in low (e.g., ~25% for 1-acyl-*sn*-glycerols)[12] to moderate (e.g., ~54–70% for 1-alkyl-*sn*-glycerols)[14] yields.

As part of our studies on the development of new synthetic methodologies for glycerolipids based on glycidol derivatives, we developed a very efficient synthesis of 2-acylglycerols via opening of the oxirane system of glycidyl esters using trifluoroacetic anhydride (TFAA).[15] Here, we report that opening the oxirane system in acyl glycidols with TFAA in the presence of trifluoroacetate anions can be carried out without concomitant acyl group migration, thus providing an efficient entry to 1-acyl glycerols.

First, opening of the oxirane ring of acyl glycidols was investigated on racemic glycidyl oleate (all compounds as in Scheme 1, but racemic). It was found that in THF/CH_2Cl_2 (1:1, v/v) at 80 °C, in the presence of TFAA (2 equiv) and tetrabutylammonium trifluoroacetate ($Bu_4N^+TFA^-$, 3 equiv) glycidyl oleate was quantitatively converted within 5 h into racemic 1-oleoyl-2,3-bis(trifluoroacetyl) glycidol (TLC, ^{1}H and ^{13}C NMR analyses). The reaction seemed to be rather general as other glycidol derivatives (linoleoyl, palmitoyl, stearoyl, benzoyl-, isopropyl-, or methyl) also underwent quantitative conversions into the corresponding bis(trifluoroacetates) without detectable migration of the fatty acid residues from C-1 to C-2.

Since trifluoroacetate esters are known to undergo smooth transesterification with alcohols,[15,16] the bis(trifluoroacetates) of type **5**, obtained in CH_2Cl_2/pentane were treated (20 min) with pyridine (10 equiv) and methanol (250 equiv) to provide racemic 1-acylglycerols.



Scheme 1. Reagents and conditions: (i) *step A*: $Bu_4N^+TFA^-$ (3.0 equiv)/TFAA (2.0 equiv), THF/CH_2Cl_2 = 1:1, v/v, 80 °C, ~5 h; (ii) *step B*: pyridine (10 equiv)/MeOH (250 equiv), CH_2Cl_2/pentane, rt, ~20 min.

Having developed the reaction conditions for the conversion of acyl glycidols into 1-acylglycerols, the reactions were next carried out on enantiomerically pure glycidol derivatives, to investigate the stereochemical outcome of this transformation (Scheme 1). *S*-(+)-Glycidol oleate **1** and *R*-(−)-glycidol oleate **2** were subjected separately to treatment as above, with TFAA and $Bu_4N^+TFA^-$ and after evaporation of the solvents and passing a solution of the residue in toluene through a small silica gel pad to remove the trifluoroacetate salt, bis(trifluoroacetate) derivatives **5** and **6**, respectively, were obtained in excellent yields. ^{1}H and ^{13}C NMR analyses confirmed[17] that opening of the oxirane system occurred with complete regioselectivity and the optical rotations measured indicated the stereospecificity of this process.

Conjugates **5** and **6** were then subjected to deprotection with methanol and pyridine as described above, and after removal of all volatile materials under vacuum, isomerically homogenous 1-oleoyl-*sn*-glycerol **9** and 3-oleoyl-*sn*-glycerol **10** (purity >99%, ^{1}H and ^{13}C NMR spectroscopy) were obtained in >90% overall yields. Since compound **9**, obtained from *S*-(+)-glycidol **1**, was identified as 1-acyl-*sn*-glycerol, and compound **10**, obtained from *R*-(−)-glycidol **2**, was identified as 3-acyl-*sn*-glycerol, this established the overall transformation to have occurred with complete retention of configuration at the C-2 carbon of the glycerol backbone.

We also found that the reagent system TFAA/$Bu_4N^+TFA^-$ opens the oxirane system of alkyl glycidols completely regioselectively and stereospecifically, as exemplified by the efficient conversion of *S*-(+)-hexadecyl glycidol **3** into 1-hexadecyl-*sn*-glycerol **11** (94% yield) with the intermediacy of bis(trifluoroacetyl) derivative **7**, and *R*-(−)-hexadecyl glycidol **4** into 1-hexadecyl-*sn*-glycerol **12** (92% yield) with the intermediacy of bis(trifluoroacetyl) derivative **8**.

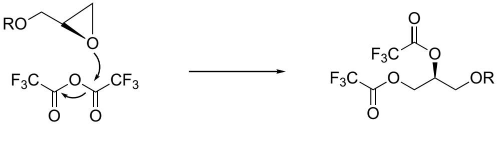
We carried out also some additional experiments to provide evidence on a possible mechanism for this transformation. Thus, ^{1}H and ^{13}C NMR spectroscopy revealed that TFAA alone effected opening of the oxirane system of acyl glycidols of type **1** with migration of the acyl group to produce the corresponding 2-acyl glycerols, while alkyl glycidols of type **3**, were completely stable under these conditions.[15] On the other hand, in the absence of TFAA, oleoyl glycidol **1** underwent reaction with tetra-*n*-butylammonium trifluoroacetate to produce, after deprotection of the trifluoroacetyl groups, a mixture of 1-monoacylglycerol **9** and 2-acylglycerol in a ratio of 85:15. In all instances where instead of TFAA, other carboxylic acid anhydrides (e.g., acetic or benzoic anhydride) with a controlled excess (e.g., 3 equiv) of $Bu_4N^+TFA^-$ were used, the target bis(trifluoroacetates) of type **5** or **7** were identified as the only products of the reaction. Reactions with acyl donors other than that of TFAA/$Bu_4N^+TFA^-$ were sluggish and are impractical, since even for a rather reactive reagent system, for example, tetra-*n*-butylammonium acetate/acetic anhydride, the reaction occurred to only ca. 85% after 24 h.

The above observations suggest that opening of the oxirane system in acyl and alkyl glycidols probably proceeds via a one-step synchronous mechanism involving nucleophilic attack of a trifluoroacetate anion on the primary carbon of the oxirane ring, with simultaneous electrophilic catalysis exerted by TFAA, as depicted in Scheme 2. Since in this mechanism no bond breaking takes place at the chiral center of the glycidol, the transformation should be stereospecific and occur with retention of configuration. In addition, the simultaneous nucleophile and electrophile catalysis provided by this reagent system should facilitate opening of the oxirane ring and prevent an acyl migration during the course of the reaction.

In conclusion, we have developed an efficient synthetic strategy based on a novel, stereospecific transformation of chiral glycidyl derivatives possessing acyl- (e.g., **1**, **2**) or alkyl- (e.g., **3**, **4**) moieties into 1(3)-acyl- (e.g., **5**, **6**) or 1(3)-alkyl-2,3(1,2)-bis(trifluoroacetyl)-*sn*-glycerols (e.g., **7**, **8**) with complete retention of configuration, from which isomerically pure 1(3)-monoacyl- (**9**, **10**) or 1(3)-monoalkyl-*sn*-glycerols (**11**, **12**) can be retrieved directly. The main features of this new protocol are (i) highly regiospecific and practically quantitative syntheses of 1(3)-monoacyl- or 1(3)-monoalkyl-*sn*-glycerols under mild conditions; (ii) the compounds **5**–**8** and **9**–**12** produced are of high purity, which alleviates problems of additional purification, and thus the risk of acyl migration and other side-reactions is eliminated; (iii) bis(trifluoroacetates) **5**–**8** can be envisaged as either, convenient storage forms or intermediate frameworks for **9**–**12**; (iv) the novel strategy also introduces the above types of glycidyl conjugates **1**–**4** as versatile, bifunctional building blocks of potential interest for the synthesis of asymmetric lipid mediators; (v) the method makes use of commercially available reactants and it is easy to scale up.

2. General procedure for the synthesis of 5–8 and 9–12

Step A: A solution of glycidyl derivative **1**–**4** (1.00 mmol) in alcohol-free dichloromethane/THF (1:1, v/v, 2.0 mL) was added to a mixture of tetra-*n*-butylammonium trifluoroacetate (1.066 g; 3.00 mmol) and trifluoroacetic anhydride (TFAA, 0.278 mL; 2.00 mmol) in the same solvent system (3.0 mL), and the reaction was kept under argon, in a pressure-proof glass ampoule at 80 °C (bath) for 5 h. The solvents and unreacted TFAA were removed under reduced pressure (bath temp 50 °C), the residue was taken up in 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 product were combined, the solvent was removed under reduced pressure, and the residue was kept under high vacuum at room temperature for 2–3 h to provide bis(trifluoroacetate) **5**–**8** (purity >99%, ^{1}H NMR spectroscopy).



R = $C_{17}H_{33}CO$; $C_{16}H_{33}$

Scheme 2.

Step B: To a solution of **5**–**8** in pentane/CH_2Cl_2 (3:1, v/v, 5.0 mL), a mixture of pyridine (0.8 mL, 10 mmol) and methanol (10.1 mL, 250 mmol) in the same solvent system (5.0 mL) was added at 0 °C and the reaction was left at room temperature for 20 min. The 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 glycerol-derivative **9**–**12** (purity >99%, ^{1}H NMR spectroscopy).

2.1. 1-Oleoyl-2,3-bis(trifluoroacetyl)-*sn*-glycerol 5

Obtained from (*S*)-(+)-2-(oleoyloxymethyl)oxirane (**1**; 0.338 g; 1.00 mmol). Yield: 0.532 g (97%, yellowish oil); R_f (pentane/toluene/EtOAc = 40:50:10, v/v/v) = 0.60; $[\alpha]_D^{20}$ −3.49 (*c* 10.14, $CHCl_3$). Anal. Calcd for $C_{25}H_{38}O_6F_6$ (548.57): C, 54.74; H, 6.98. Found: C, 54.64; H, 7.03. ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz): 0.88 (t, $J = 6.6$ Hz, 18-CH_3, 3H); 1.30 (m, 4-7-CH_2, 12-17-CH_2, 20H); 1.62 (m, 3-CH_2, 2H); 2.02 (m, 8-CH_2, 11-CH_2, 4H); 2.34 (t, $J = 7.5$ Hz, 2-CH_2, 2H); 4.25 (dd, $J = 6.0$, 5.9 Hz, $RC(O)OCH_aH_bCHCH_2OC(O)$, 1H); 4.48 (dd, $J = 4.2$, 4.0 Hz, $RC(O)OCH_aH_bCHCH_2OC(O)$, 1H); 4.54 (dd, $J = 6.6$, 6.6 Hz, $C(O)OCH_2CHCH_aH_bOC(O)CF_3$, 1H); 4.66 (dd, $J = 3.5$, 3.7 Hz, $C(O)OCH_2CHCH_aH_bOC(O)CF_3$, 1H); 5.35 (m, $CH{=}CH$, 2H); 5.51 (m, $OCH_2CHOC(O)CF_3$, 1H). ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz): 14.30 (18-CH_3); 22.89 (17-C); 24.92 (3-C); 27.36, 27.43 (11-C, 8-C); 29.22–29.98 (4-C-7-C, 12-C-15-C); 32.12 (16-C); 33.99 (2-C); 129.90, 130.26 (9-C, 10-C); 173.16 (1-C): oleoyl fragment; 114.44 (d, $J = 285.3$ Hz, 2-C); 156.85 (d, $J = 43.5$ Hz, 1-C): trifluoroacetyl fragment; 60.81 (1-C); 64.69 (3-C); 72.58 (2-C): glycerol fragment.

2.2. 3-Oleoyl-1,2-bis(trifluoroacetyl)-*sn*-glycerol 6

Obtained from (*R*)-(−)-2-(oleoyloxymethyl)oxirane (**2**; 0.338 g; 1.00 mmol). Yield: 0.521 g (95%, yellowish oil). While all other physicochemical and spectral characteristics were identical with those of **5**, $[\alpha]_D^{20}$ +3.54 (*c* 11.28, $CHCl_3$).

2.3. 1-Hexadecyl-2,3-bis(trifluoroacetyl)-*sn*-glycerol 7

Obtained from (*S*)-(+)-2-(hexadecyloxymethyl)oxirane (**3**; 0.299 g; 1.00 mmol). Yield: 0.468 g (92%, colourless oil); R_f (pentane/toluene/EtOAc = 40:50:10, v/v/v) = 0.76; $[\alpha]_D^{20}$ −9.55 (*c* 10.89, $CHCl_3$). Anal. Calcd for $C_{23}H_{38}O_5F_6$ (508.53): C, 54.32; H, 7.53. Found: C, 54.40; H, 7.47. ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz): 0.88 (t, $J = 6.6$ Hz, 16-CH_3, 3H); 1.26 (m, 3-15-CH_2, 26H); 1.55 (m, 2-CH_2, 2H); 3.46 (m, 1-CH_2, 2H); 3.67 (dd, $J = 2.2$, 2.2 Hz, $C(O)OCH_2CHCH_aH_bOR$, 2H); 4.57 (dd, $J = 6.8$, 6.8 Hz, $ROCH_2CHCH_aH_bOC(O)CF_3$, 1H); 4.67 (dd, $J = 3.1$, 3.1 Hz,

$ROCH_2CHCH_aH_bOC(O)CF_3$, 1H); 5.42 (m, $OCH_2CHOC(O)CF_3$, 1H). ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz): 14.30 (16-CH_3); 22.90 (15-C); 26.13 (3-C); 29.57–29.90 (4-C-14-C); 32.14 (2-C); 72.39 (1-C): hexadecyl fragment; 114.51 (q, $J = 283.1$ Hz, 2-C); 157.12 (q, $J = 20.6$ Hz, 1-C): trifluoroacetyl fragment; 65.35 (3-C); 67.72 (1-C); 73.76 (2-C): glycerol fragment.

2.4. 3-Hexadecyl-1,2-bis(trifluoroacetyl)-*sn*-glycerol 8

Obtained from (*R*)-(−)-2-(hexadecyloxymethyl)oxirane (**4**; 0.299 g; 1.00 mmol). Yield: 0.478 g (94%, colourless oil). With the exception of $[\alpha]_D^{20}$ +9.67 (*c* 10.03, $CHCl_3$), all other physicochemical and spectral characteristics were identical with those of **7**.

2.5. 1-Oleoyl-*sn*-glycerol 9

Obtained from (*S*)-(+)-2-(oleoyloxymethyl)oxirane (**1**; 0.338 g; 1.00 mmol) via **5**. Yield: 0.338 g (95%, calculated on **1**); white solid; mp 34.5–36 °C (identical with that of a commercial sample from Fluka); R_f (pentane/toluene/EtOAc = 30:20:50, v/v/v) = 0.34; $[\alpha]_D^{20}$ −1.32 (*c* 11.76, $CHCl_3$). Anal. Calcd for $C_{21}H_{40}O_4$ (356.54): C, 70.74; H, 11.31. Found: C, 70.66; H, 11.40. ^1H NMR δ_H (in ppm, $CDCl_3$, 400 MHz): 0.87 (t, $J = 6.6$ Hz, 18-CH_3, 3H); 1.28 (m, 4-7-CH_2, 12-17-CH_2, 20H); 1.62 (m, 3-CH_2, 2H); 2.00 (m, 8-CH_2, 11-CH_2, 4H); 2.34 (t, $J = 7.5$ Hz, 2-CH_2, 2H); 2.92 (br s, OH, 2H); 3.59 (dd, $J = 5.9$, 5.9 Hz, $C(O)OCH_2CHCH_aH_bOH$, 1H); 3.69 (dd, $J = 3.8$, 4.0 Hz, $C(O)OCH_2CHCH_aH_bOH$, 1H); 3.93 (m, OCH_2CHOH, 1H); 4.16 (m, $C(O)OCH_aH_bCHCH_2OH$, 2H); 5.34 (m, $CH{=}CH$, 2H). ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz): 14.32 (18-CH_3); 22.89 (17-C); 25.11 (3-C); 27.37, 27.43 (11-C, 8-C); 29.30–29.98 (4-C-7-C, 12-C-15-C); 32.12 (16-C); 34.36 (2-C); 129.93, 130.26 (9-C, 10-C); 174.53 (1-C): oleoyl fragment; 63.56 (3-C); 65.39 (1-C); 70.48 (2-C): glycerol fragment.

2.6. 3-Oleoyl-*sn*-glycerol 10

Obtained from (*R*)-(−)-2-(oleoyloxymethyl)oxirane (**2**; 0.338 g; 1.00 mmol) via **6**. Yield: 0.335 g (94%). Identical physicochemical and spectral characteristics with those of **9**. $[\alpha]_D^{20}$ +1.28 (*c* 10.64, $CHCl_3$); $[\alpha]_D^{20}$ −3.33 (*c* 7.33, pyridine); lit.[9] $[\alpha]_D^{22}$ −3.2 (*c* 5, pyridine).

2.7. 1-Hexadecyl-*sn*-glycerol 11

Obtained from (*S*)-(+)-2-(hexadecyloxymethyl)oxirane (**3**; 0.299 g; 1.00 mmol) via **7**. Yield: 0.297 g (94%); white solid; mp 62.9–63.9 °C; lit.[14] mp 63.0–64.0 °C; R_f (pentane/toluene/EtOAc = 30:20:50, v/v/v) = 0.26; $[\alpha]_D^{20}$ −2.10 (*c* 3.00, THF); lit.[14] $[\alpha]_D^{25}$ −2.68 (*c* 3.5, THF). Anal. Calcd for $C_{19}H_{40}O_3$ (316.52): C, 72.10; H, 12.74. Found: C, 72.00; H, 12.80. ^1H NMR δ_H (in ppm, $CDCl_3$, 400 MHz): 0.88 (t, $J = 7.1$ Hz, 16-CH_3, 3H); 1.25 (m, 3-15-CH_2, 26H); 1.57 (qnt, $J = 7.5$ Hz, 2-CH_2, 2H); 2.30 (br s, OH, 2H); 3.40–3.57 (m, overlapping with dd, 1-CH_2, $OCH_2CHCH_aH_bOH$, 4H); 3.64 (dd, $J = 5.1$, 5.1 Hz, $OCH_2CHCH_aH_bOR$, 1H); 3.72 (dd, $J = 3.8$, 3.8 Hz, $OCH_2CHCH_aH_bOR$, 1H); 3.85 (m, OCH_2CHOH, 1H). ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz): 14.33 (16-CH_3); 22.91 (15-C); 26.30 (3-C); 29.58–29.91 (4-C-14-C); 32.14 (2-C); 72.77 (1-C): hexadecyl fragment; 64.55 (3-C); 70.60 (2-C); 72.09 (1-C): glycerol fragment.

2.8. 3-Hexadecyl-*sn*-glycerol 12

Obtained from (*R*)-(−)-2-(hexadecyloxymethyl)oxirane (**4**; 0.299 g; 1.00 mmol) via **8**. Yield: 0.291 g (92%). Identical physicochemical and spectral characteristics with those of **11**. $[\alpha]_D^{20}$ +2.72 (*c* 3.66, THF); lit.[14] $[\alpha]_D^{25}$ +2.69 (*c* 3.5, THF).

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