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A short highly regio- and stereoselective synthesis of triacylglycerols

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(Received December 14th, 1990; revision received January 11th, 1991; accepted January 11th, 1991)

Glycidyl esters reacted with carboxylic anhydrides in the presence of LiBr in tetrahydrofuran (THF) or benzene to produce 3-bromo-1,2-propanediol esters with no significant acyl migration. Displacement of Br by cesium carboxylates was accomplished cleanly in THF-hexamethylphosphoric triamide (THF-HMPT) at 50–55°C (5 h) completing a highly regioselective triglyceride synthesis. The regioselectivity of these reactions allows stereoselective synthesis if one initiates the short sequence with enantiomerically pure glycidol. Commercial (*R*)-(+)-glycidol (94.6% *R*) was used to synthesize (*R*)- and (*S*)-lauroyl oleoyl palmitoyl glycerol. ¹H-NMR data of *S*-methoxy- α -trifluoromethylphenyl acetic acid ((*S*)-MTPA) derivatives formed by reaction of the (*S*)-MTPA ester of (*R*)-glycidol indicated that these reactions preserved configuration as expected.

Keywords: diacylglycerols; triacylglycerols; glycidol; stereochemical analysis; stereoselective synthesis.

Introduction

We required configurationally pure triglycerides for research dealing with lipases. Until recently, the most commonly employed strategy for their synthesis involved periodic acid cleavage of 1,2,5,6-diisopropylidene D-mannitol which yields two equivalents of (*S*)-1,2-isopropylidene glycerol that can then be used conveniently to prepare, for example, (*S*)-1-acylglycerols (also referred to as 3-acyl-*sn*-glycerols) [1,2]. Additional useful transformations that require chiral isopropylidene glycerols have been reported [3,4]. A complementary approach has been described starting with 3,4-isopropylidene-D-mannitol [5], and yet another related route was initiated from L-arabinose [6]. These approaches to triglycerides have in common the generation of a configurationally pure 1,2-isopropylidene glycerol that can be elaborated

to 1,3-diacyl glycerols usually involving chromatographic purification to separate from byproducts, e.g. 1,2-isomer and the triglyceride. Alternatively, the configurationally pure 1-acyl glycerol is silylated at the other primary position, acylated at the 2-position, then deprotected using NBS in DMSO to generate the 1,2-diacyl glycerol [7]. This material can then be converted to the triglyceride although acyl migration can still be a problem.

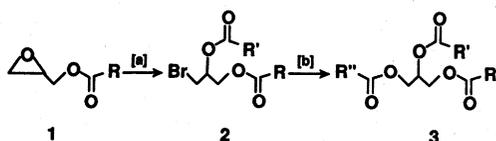
Availability of glycidol enantiomers in high configurational purity [8] has inspired further efforts to secure configurationally pure acylated glycerols and related compounds by less arduous routes. Thus the epoxide ring of (*S*)-glycidol was cleaved in the presence of stearic acid assisted by titanium (IV) to produce (*S*)-1-stearoyl glycerol [9]. A similar transformation converted the tosylate, or *t*-butyldiphenylsilyl ether, of (*R*)- or (*S*)-glycidol to primary hexadecyl ethers using BF₃-etherate with 1-hexadecanol [10]. These cleavages occurred with high regioselectivity and stereointegrity. Related reactions with glycidol and glycidol derivatives using fatty acids and anhydrides with catalysts have been reported though regiospecificity for epoxide

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cleavage was not an issue [11–14]. Reaction of a chiral glycidol tosylate with potassium methyl xanthate, however, apparently did yield an adduct with clean inversion of the secondary carbon of glycidol [15].

Results and Discussion

We report here a complementary reaction sequence that is particularly useful for triglycerides and is quite brief. Glycidyl esters **1** reacted with carboxylic anhydrides in the presence of LiBr in THF or benzene to produce 3-bromo-1,2-propanediol diesters **2** without significant acyl migration (Scheme I). We initially selected three carboxylic acids whose acyl carbons would be distinguishable by ^{13}C -NMR and, furthermore, could be differentiated according to their position (primary or secondary) on glycerol (Table I). The acids were *n*-octanoic, phenylacetic, and pivalic. The reactions of the glycidyl esters were highly regioselective; that is to say, less than 3% intercontamination observed which is the limit of ^{13}C analysis. The reaction probably proceeds with catalysis by a small amount of the free acid present, and as long as the anhydride was not sterically hindered, namely pivalic anhydride, the intermediate bromohydrin esterified with minimal acyl migration. It should be noted, however, that distillation of **2** caused 1,2 bromine-



	R	R'	R''
1a	C ₇ H ₁₅		
b	CH ₂ C ₆ H ₅		
c	t-Bu		
d	(S)-MTB		
2a	C ₇ H ₁₅	CH ₂ C ₆ H ₅	
b	CH ₂ C ₆ H ₅	C ₇ H ₁₅	
c	t-Bu	C ₇ H ₁₅	
d	(S)-MTB	C ₇ H ₁₅	
3a	C ₇ H ₁₅	CH ₂ C ₆ H ₅	t-Bu
b	CH ₂ C ₆ H ₅	C ₇ H ₁₅	t-Bu
c	(S)-MTB	C ₇ H ₁₅	C ₇ H ₁₅

[a] = LiBr, R'CO₂OCR', THF, 25°C.

[b] = Cs₂CR'', THF-HMPT, 45–50°C.

Scheme I.

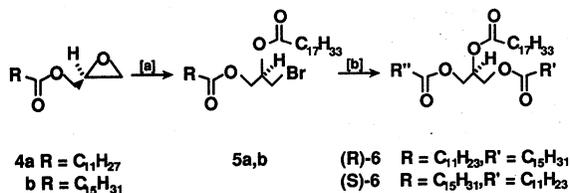
TABLE I

^{13}C -NMR shifts for acyl carbons

Compound	Glycerol carbon	
	1 (3)	2
Trioctanoin	173.21	172.80
Triphenylacetoin	170.85	170.52
Tripivaloin	177.82	177.32
2a	173.01	170.40
2b	170.85	172.52
2c	177.67	172.55
5a	173.06	172.60
5b	173.00	172.56
3a	173.11 (177.74)	170.46
3b	170.84 (177.67)	172.58
6	172.67	173.10

acyl exchange as determined by both GLC and ^{13}C -NMR. In the final step the bromine of **2** was displaced using the cesium salt of the third acid residue [16]; this transformation occurred cleanly in THF-HMPT at 45–50°C with all three acids as judged by ^{13}C -NMR spectra of chromatographically pure products. Thus **2b** + cesium pivalate, and **2c** + cesium phenylacetate each gave pure **3b**. It should be noted that neither the **2a-2b**, nor the **3a-3b**, isomeric pairs were resolved by GLC or HPLC, and that this would be the case for biologically more important fatty acid analogs. Hence the use of ^{13}C -NMR tests this reaction sequence uniquely.

The regioselectivity of these reactions ensures stereoselective synthesis if one initiates the short sequence with enantiomerically pure glycidol. Racemization could only occur if the secondary C—O bond were ruptured or 1,3-acyl migration occurred. Neither is expected, and the high regioselectivity observed is consistent with expectation of configuration retention. Nevertheless, additional information was sought to validate the idea. (*R*)-(+)-Glycidol was converted to its (*S*)-MTPA (α -methoxy- α -trifluoromethylphenyl acetic acid) ester [17] and judged to be 94.6% (*R*), i.e., 89.2% ee, by its ^1H -NMR spectrum (see Experimental). This glycidic ester was then treated with octanoic anhydride and LiBr to generate a bromodiester analog, **2d**. The bromine was displaced using cesium octanoate producing a triglyceride, **3c**. The ^1H -



Scheme II. [a], [b]: see scheme I.

NMR spectra of these compounds indicated preservation of the chiral center (see Experimental). With these procedures in hand we exemplified the procedure by preparing (*R*)- and (*S*)-lauroyl oleoyl palmitoyl glycerol from (*R*)-glycidol (Scheme II). (*R*)-Glycidyl laurate and palmitate **4** were converted to the corresponding bromodiesters **5** with oleic anhydride and LiBr. Displacement of bromide with the appropriate cesium salt led to the enantiomeric triglycerides **6**. The reactions are facile, very regioselective, preserve configuration, and proceed in high yield.

Materials and Methods

General procedures and reagents

Melting points are uncorrected. Silica gel TLC plates of 0.25 mm thickness from Analtech, Inc. were used to monitor reactions with iodine vapor or bromthymol blue spray for visualization. Kodak silica gel (60–200 mesh) was used for preparative column chromatography. Solvents were purchased from Burdick and Jackson excepting that THF and HMPT were obtained from Aldrich Chem. Co. and dried before use. The THF was distilled from LAH; HMPT was stored over 13 Å molecular sieves. Reagents were purchased from Aldrich Chem. Co. or Ventron Corp. and used directly. (*R*)-(+)-Glycidol [α]_{D18} = +12° (neat) was obtained from Aldrich Chem. also; it was 94.6% (*R*) judged by the ¹H-NMR of its (*S*)-MTPA ester [9]. Cesium salts were prepared from Cs₂CO₃ and the corresponding acid in benzene, azeotropically removing water. Homogeneous triglycerides, glycidyl esters and carboxylic anhydrides were prepared by conventional methods and gave satisfactory spectral data after distillation or column chromatography.

Gas-liquid chromatography was performed with a Shimadzu GC-Mini-2 instrument using an SPB-1 column (0.25 mm × 30 m) with a 50:1 split ratio and He as carrier gas. Infrared data were recorded with a Perkin Elmer 1310 Spectrophotometer using 3% CCl₄ solutions. NMR spectra (¹³C and ¹H) were obtained with a JEOL JNM-GX400 FT-NMR spectrometer with CDCl₃ solvent and tetramethylsilane as the reference. Mass spectra were obtained with a Hewlett-Packard HP-5995 GC/MS system employing an OV-1 column (0.25 mm × 30 mm). Combustion analyses were carried out by Micro-Analysis, Inc., Wilmington, DE.

3-Bromo-1,2-propanediol diesters, 2 and 5. The glycidyl ester, **1** or **4** (6.2 mmol), was added to a stirred and cooled (0–5°C) mixture of carboxylic anhydride (6.3 mmol) and LiBr (1.7 g, 19 mmol) in benzene (15 ml). The resulting mixture was stirred overnight at ambient temperature and was then worked up by dilution with ether and washing successively with 1.25 N NaOH and H₂O. After drying (MgSO₄), the solvent was removed, and since we had observed isomerization when we distilled **2c**, the residual oil was chromatographed on silica gel (20 g) eluting with 5–10% ether-hexane. Removal of solvent gave 85–90% yields of **2** and **5**.

Compound 2a. TLC (15% ethyl acetate-hexane) *R*_f = 0.37; GLC (240°C) *k*' = 6.4; IR: 3020, 1740 cm⁻¹; ¹H-NMR δ 7.2 (m, aryl H, 5H), 5.14 (m,

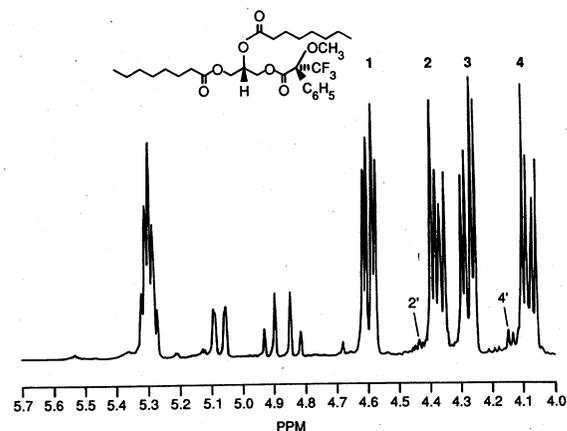


Fig. 1. Portion of ¹H-NMR spectrum indicating diastereomeric purity of **3c**: 1 and 2 are H_{1a} and H_{1b}, 3 and 4 are H_{3a} and H_{3b}, 2' is H_{1a} of the diastereomer; 4' is H_{3a} of the diastereomer (see Materials and Methods).

HCO, 1H), 4.27 and 4.16 (m, H₂CO, 2H), 3.59 (s, PhCH₂C=O, 2H), 3.42 (m, CH₂Br, 2H), 2.18 (t, J = 7.6 Hz, CH₂C=O, 2H), 1.50 (m, CH₂, 2H), 1.21 (bs, CH₂, 8H), 0.81 (t, J = 6.8 Hz, CH₃, 3H) ppm; ¹³C-NMR δ 173.0, 170.4, 133.3, 129.1, 128.5, 127.1, 70.4, 62.7, 41.0, 33.8, 31.5, 29.5, 28.9, 28.8, 24.7, 22.5, 13.9 ppm; MS 70eV *m/e* (rel. int.) 127 [C₇H₁₅C=O⁺] (0.13), 118 [PhCH₂C=OH⁺] (1.00), 91 [PhCH₂⁺] (0.66). Anal. Calcd for C₁₉H₂₇BrO₄: C, 57.15; H, 6.81; Br, 20.01. Found: C, 57.29; H, 6.72; Br, 19.35.

Compound 2b. TLC, GLC, IR, ¹H-NMR, and MS as for **2a**; ¹³C-NMR δ 172.5, 170.7, 133.5, 129.1, 128.5, 127.1, 69.6, 63.3, 41.0, 34.0, 31.5, 29.6, 28.9, 28.7, 24.7, 22.5, 13.9.

Compound 2c. TLC (15% ethyl acetate-hexane) *R_f* = 0.46; GLC (220°C) *k'* = 2.90; IR: 1740 cm⁻¹; ¹H-NMR δ 5.23 (m, HCO, 1H), 4.33, 4.20 (2dd, H₂CO, 2H), 3.50 (m, CH₂Br, 2H), 2.33 (m, CH₂C=O, 2H), 1.62 (m, CH₂, 2H), 1.27 (m, CH₂), and 1.20 (s, CH₃) total 16–17H, 0.81 (m, CH₃, 3H) ppm; ¹³C-NMR δ 177.7, 172.6, 69.8, 63.0, 38.7, 34.0, 31.5, 29.8, 28.9, 28.8, 27.0, 24.8, 22.5, 13.9 ppm; MS 70 eV *m/e* (rel. int.) 127 [C₇H₁₅C=O⁺] (0.71), 85 [t-BuC=O⁺] (1.00).

Compound 5a. TLC (15% ethyl acetate-hexane) *R_f* = 0.44; IR: 1740 cm⁻¹; ¹H-NMR δ 5.27 (bs, HC=CH, 2H), 5.14 (m, HCO, 1H), 4.28 and 4.16 (2dd, J[H_{1a}—H_{1b}] = 11.9 Hz, J[H_{1a}—H₂] = 5.6 Hz, J[H_{1b}—H₂] = 4.3 Hz, H₂CO, 2H), 3.44 (2dd, J[H_{3a}—H_{3b}] = 10.9 Hz, J[H_{3a}—H₂] = 5.5 Hz, J[H_{3b}—H₂] = 5.5 Hz, H₂CBr, 2H), 2.26 (q, J = 7.3 Hz, CH₂C=O, 4H), 1.95 (m CH₂C=C, 4H), 1.56 (m, CH₂, 4H), 1.20 (bs, CH₂, 35–36H), 0.81 (t, J = 6.7 Hz, CH₃, 6H) ppm; ¹³C NMR δ 173.1, 172.6, 129.9, 129.6, 69.8, 62.9, 34.1, 34.0, 31.9, 29.8, 29.7, 29.64, 29.57, 29.47, 29.41, 29.28, 29.11, 29.05, 29.0, 27.15, 27.09, 24.8, 22.6, 14.1 ppm; MS 70eV *m/e* (rel. int.) 319, 321 (0.32, 0.37), 264, 265 (1.00, 0.45), 183 (0.50). Anal. Calcd for C₃₃H₆₁BrO₄: C, 65.87; H, 10.22; Br, 13.28. Found: C, 65.71; H, 9.87; Br, 13.06. Sufficiently sensitive polarimetry for **5** and **6** was not available, and stereochemical integrity is based on analogy to the other preparations for which ¹³C-NMR and MTPA derivatives indicate preservation of configuration.

Compound 5b. TLC, IR, ¹H-NMR, ¹³C-NMR the same as, or (NMR) equivalent to **5a**; MS 70eV

m/e (rel. int.) 375, 377 (0.25, 0.26), 264, 265 (1.00, 0.31), 239 (0.22). Anal. Calcd for C₃₇H₆₉BrO₄: C, 67.55; H, 10.57; Br, 12.15. Found: C, 67.59; H, 10.39; Br, 12.14.

Mosher ester (MTPA ester), 2d: (*R*)-3-bromo-1,2-propanediol, 1-(*S*)-1'-methoxy-1'-trifluoromethylphenylacetate, 2-octanoate. TLC (15% ethyl acetate-hexane) *R_f* = 0.25; IR: 1745 cm⁻¹; ¹H-NMR δ 7.41–7.51 (m's, 5H, ArH), 5.23 (m, 1H, HCO), 4.66 and 4.47 (2dd, J[H_{1A}—H_{1B}] = 12.2 Hz, J[H_{1A}—H₂] = 4.9 Hz, J[H_{1B}—H₂] = 4.3 Hz, 2H, CH₂O-MTPA), 3.54 (s, 3H, OCH₃), 3.44 and 3.39 (2dd, J[H_{3A}—H_{3B}] = 11.0 Hz, J[H_{3A}—H₂] = 4.9 Hz, J[H_{3B}—H₂] = 6.1 Hz, 2H, CH₂Br), 2.44 and 2.29 (m's, 2H, CH₂CO), 1.64 (m, 2H, CH₂), 1.27 (bs, 8–9 H, CH₂'s), 0.89 (bt, 3H, CH₃) ppm. The diastereomeric H_{1A} is partially screened appearing at 4.52 ppm allowing an estimate of < 6% of the diastereomer.

Triglycerides 3 and 6. 3-Bromo-1,2-propanediol diester, **2** or **5**, (2.5 mmol) was warmed in a mixture of 10 ml each of THF and HMPT containing the appropriate cesium carboxylate (5.0 mmol) at 45–50°C for 4–5 h, after which the product was obtained by working up with H₂O and ether. The organic phase was dried, and the solvent was removed. The product was purified by column chromatography (20 g of silica gel eluting with 10–15% ether-hexane) to yield 90–95% of the triglycerides **3** and **6**.

Compound 3a. GLC (280°C) *k'* = 2.5; IR: 1740 cm⁻¹; ¹H-NMR δ 7.2 (m, PhH, 5H), 5.24 (m, HCO, 1H), 4.24, 4.08 (2dd, H₂CO, 4H), 3.58 (s, PhCH₂, 2H), 2.20 (t, J = 7.6 Hz, CH₂C=O, 2H), 1.52 (m, CH₂, 2H), 1.23 (bs, CH₂, 8–9H), 1.10 (s, CH₃, 8–9H), 0.83 (bt, CH₃, 3H) ppm; ¹³C-NMR δ 177.7, 173.1, 170.5, 133.4, 129.1, 128.4, 127.1, 69.4, 61.9, 61.8, 41.1, 38.6, 33.8, 31.5, 28.9, 28.7, 26.9, 24.6, 22.4, 13.9 ppm; MS 70eV *m/e* (rel. int.) 127 (0.11), 118 (1.00), 91 (0.66). Anal. Calcd for C₂₄H₃₆O₆: C, 68.54; H, 8.63. Found: C, 68.23; H, 8.30.

Compound 3b. GLC, IR, ¹H-NMR and MS essentially as for **3a**; ¹³C NMR δ 177.4, 172.3, 170.6, 133.4, 129.0, 128.3, 126.9, 68.6, 62.3, 61.8, 40.8, 38.5, 33.8, 31.4, 28.8, 28.7, 26.8, 24.6, 22.3, 13.8 ppm. Anal. Calcd. for C₂₄H₃₆O₆: C, 68.54; H, 8.63. Found: C, 68.71; H, 8.49.

Compound 6. TLC (15% ethyl acetate-hexane) R_f = 0.40; IR: 1740 cm^{-1} ; $^1\text{H-NMR}$ δ 5.27 (m, HC=CH, 2H), 5.02 (m, HCO, 1H), 4.22 and 4.08 (2dd, H_2CO , 4H), 2.24 (m, $\text{CH}_2\text{C}=\text{O}$, 6H), 1.95 (m, $\text{CH}_2\text{C}=\text{C}$, 4H), 1.54 (bs, CH_2 , 2H), 1.15 (bs, CH_2 envelope), 0.81 (t, $J = 6.7$ Hz, CH_3 , 9H) ppm; $^{13}\text{C-NMR}$ δ 173.1, 172.6, 129.9, 129.6, 68.8, 62.0, 34.09, 33.94, 31.84, 31.52, 29.69, 29.63, 29.60, 29.55, 29.46, 29.40, 29.25, 29.20, 29.13, 29.03, 28.97, 27.14, 27.09, 24.8, 22.6, 14.0 ppm; MS 70eV m/e (rel. int.) 578 (0.32), 577 (0.33), 522 (0.35), 521 (0.38), 497 (0.35), 496 (1.00), 264 (0.47). Anal. Calcd for $\text{C}_{49}\text{H}_{92}\text{O}_6$: C, 75.72; H, 11.93. Found: C, 75.91; H, 11.89.

Mosher ester (MTPA ester) 3c: stereospecifically numbered-glycerol-1-(*S*)-1'-methoxy-1'-trifluoromethylphenylacetate, 2,3-dioctanoate. TLC (15% ethyl acetate-hexane) R_f = 0.22; IR: 1745 cm^{-1} ; $^1\text{H-NMR}$ δ 7.39–7.51 (ms 5H ArH), 5.29 (m, 1H HCO), 4.38 and 4.60 (2dd, $J[\text{H}_{1a}-\text{H}_{1b}] = 11.0$ Hz, $J[\text{H}_{1a}-\text{H}_2] = 6.1$ Hz, $J[\text{H}_{1b}-\text{H}_2] = 4.3$ Hz, 2H, CH_2OMTPA), 4.08 and 4.28 (2dd, $J[\text{H}_{3a}-\text{H}_{3b}] = 12.2$ Hz, $J[\text{H}_{3a}-\text{H}_2] = 4.9$ Hz, $J[\text{H}_{3b}-\text{H}_2] = 4.9$ Hz, 2H, $\text{CH}_2\text{O-octanoyl}$), 3.53 (s, 3H, OCH_3), 2.31 (m, 4H, $\text{CH}_2\text{C}=\text{O}$), 1.61 (m, 4H, CH_2), 1.27 (bs, 16.2H, CH_2 envelope), 0.88 (bt, 6H, CH_3) ppm. The diastereomeric H_{1a} and H_{3a} are partially obscured appearing at 4.43 and 4.14 ppm respectively; indications are that the material retained its degree of diastereomeric purity.

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