A New Strategy to Synthesize Pure Mixed Diglycerides

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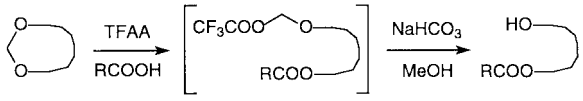
Abstract: The acylolytic cleavage of glycerol methylene acetals with fatty acids provides a new synthetic strategy that leads to pure mixed 1,2-diglycerides.

Key words: methylene acetals, acylation, glycerol



Scheme 1

Diglycerides are important bioagents, precursors of triglycerides, of phospholipids[1] and of glycolipids.[2] The symmetrical or asymmetrical monoacid diglycerides are relatively easy to prepare and the 1,3-isomer usually crystallizes. The mixed asymmetrical diglycerides are more difficult to obtain, particularly as a single isomer. Various approaches have been developed that mostly used protected forms of glycerol such as the carbonate,[3] or protected forms of solketal: trityl-,[4] benzyl-,[5] MEM-ether.[6] Several protected forms of glycidol have also been used as sources of diglycerides: ester,[7] levulinate,[8] trityl-,[9] and silyl ether.[10]

These classical strategies employed the chemoselective esterification of a primary *vs* a secondary alcohol[11] or protection/deprotection sequences on hydroxyl groups. During these synthetic operations the migration of a fatty chain from the internal (2) position to an external (1 or 3) position, or equilibrium leading to mixtures of isomers, plagued most syntheses of pure diglycerides. Chemists have thus focused their interest on the use of specific methods that would limitate the phenomenon of acyltropy.[12, 13]

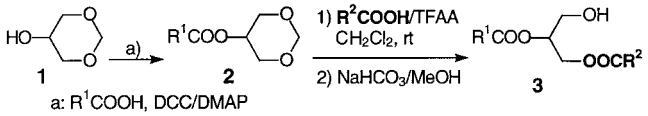
We describe herein a new strategy aimed at the synthesis of mixed asymmetric diglycerides (1,2-diglycerides) that affords pure compounds. The strategy is based on the specific properties of methylene acetals, a protecting group never used in glycerolipid chemistry.

We have shown that the cleavage of glycerol acetals by an acyl ion (acylolysis) was a convenient method for the synthesis of pure mixed triglycerides.[14] It made possible the double connection of a fatty chain directly onto the protected diol synthon of glycerol monoesters. For the synthesis of diglycerides we took advantage of the specific reactivity of methylene acetals that allowed desymmetrization of the two oxygen atoms forming the acetal bridge (Scheme 1).

The mixture of a carboxylic acid and trifluoroacetic anhydride (TFAA) generates a mixed anhydride that cleaves a methylene acetal moiety to an ester and a trifluoroacetoxy methyl ether. This latter function can be selectively hydrolyzed or methanolyzed to the alcohol, and the overall process leads to a hydroxyl ester.[15]

We have applied this new strategy to the synthesis of fatty esters of 5-hydroxy-1,3-dioxane (**1**). Methyleneglycerol **1** can be selectively prepared by transacetalization of glycerol and dimethoxymethane[16] or by chemoselective reactions of glyphoral.[17] Esterification of the secondary alcohol in **1** with a fatty acid R^1COOH and dicyclohexylcarbodiimide (DCC) in the presence of 4-dimethylaminopyridine (DMAP) afforded dioxane esters **2** (table).

The methylene acetal function of ester **2** underwent an acylolytic cleavage upon reaction with TFAA and a second fatty acid R^2COOH, 2.2 equivalents of each at room temperature. The slow reaction, between 1 and 5 days, was finally quenched by selective methanolysis of the stable trifluoroacetate intermediate, to give hydroxyl ester **3** in fairly good yields (table method A).[18]



Scheme 2

The mild experimental conditions for the initial methylene acetal cleavage and for the final methanolysis allowed the formation of pure mixed diglycerides **3**, as indicated by their NMR spectra. NMR is suitable to identify and to determine the purity of the diglycerides.[19] The chemical shifts of protons and carbons are nearly unaffected of the nature of the attached acyl chains. Therefore 1,2- and 1,3-diglycerides display a characteristic NMR spectrum for the protons and carbons of the glyceryl backbone.[20] Only in the case of short chains (C_2, C_5) have we observed traces of the 1,3-isomer (<5%).

The reaction was possible in the presence of an unsaturation. When R^1 was unsaturated, the reaction simply re-

Table Synthesis of asymmetric mixed 1,2-diglycerides **3** from **2** in the presence of Triflic anhydride (Method A: without BF_3•OEt_2 activation; method B: with BF_3•OEt_2)

	R^1COOH		**2** %	R^2COOH	time (h) A	B	**3** % A	B
a	valeric	C_4H_9COOH	80	AcOH	18	2	90	83
b	"			capric	17	2	74	80
c	"			palmitic	66	2	68	82
d	"			behenic	144	2	69	80
e	capric	$C_9H_{19}COOH$	82	palmitic	91	2	73	81
f	"			behenic	74	2	76	82
g	palmitic	$C_{15}H_{31}COOH$	93	capric	118	2	84	84
h	"			behenic	21	2	83	83
i	behenic	$C_{21}H_{43}COOH$	80	palmitic	87	2	73	80
j	$C_8H_{17}CH{=}CH(CH_2)_7COOH^*$		92	palmitic	112	2	83	
k	$CH_2{=}CH(CH_2)_8COOH^{**}$		89	palmitic	72	2	88	

*: oleic; **: undecylenic

quired 3 equiv of the next fatty acid R^2COOH. When this second acid was unsaturated, the acylolysis was also possible but was too slow to be of practical interest. We related these behaviors to complexation between the double bond and the acyl ion that initiates the cleavage. The reaction is not applicable in the presence of other functional groups such as an alcohol (12-hydroxy stearic acid) or a pyridine (nicotinic acid) that directly reacted with the acylolyzing agent.

Methylene acetals are much more stable than the corresponding ketals and their cleavage was comparatively slower. This fact and the stability of the trifluoroacetoxy methyl ether intermediate, allowed to stop the acylolysis at this stage thus differentiating the oxygens. Although the reaction could be accelerated by gentle warming to 40 °C, acyltropy increased up to 25% in the case of esters with a short chain like a valerate. Simple acetolysis of sugars has been effected with Ac_2O in the presence of BF_3•OEt_2.[21] We envisaged that the use of this Lewis acid might accelerate the current generalized acylolysis either by activating the reagent or by neutralizing the electron rich carbonyl group of the secondary fatty ester in **2**.

Thus, BF_3•OEt_2 (0.1 equiv) was mixed with dioxane ester **2** before addition of the acylolyzing mixture. The results reported in the Table are striking: all the reactions involving saturated acids were completed within 2 h using method B. Moreover, only 1.1 equiv of the acid was needed, and the yields were comparable with (or even improved) the non-activated procedure (Table; method B). The diglycerides were obtained with the same purity, i.e. only trace amounts of the 1,3-isomer in a few cases. However, the BF_3•OEt_2 activation was not applicable to unsaturated compounds due to substantial degradation of the olefin, both in the acid and in the target glyceride.

In conclusion we have described the acylolytic cleavage of methylene acetals by a fatty acid combined to TFAA. This reaction, activated or not by BF_3•OEt_2, provides a new strategy for the synthesis of mixed 1,2-diglycerides when applied to the dioxane isomer of glycerol formals. The method is simple, applicable to saturated and unsaturated fatty chains, and affords topologically pure glycerides.

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(18) *General procedure for the acylolysis of dioxane ester **2** to diglyceride **3** (method A):* The dioxane ester **2** (0.5 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL). TFAA (1.1 mmol or 1.65 mmol for unsaturated esters) then the fatty acid (1.1 or 1.65 mmol) were added at 0 °C under argon. The ice bath was removed after 10 min and the solution was stirred at rt until no starting material was left. The reaction flask was cooled to 0 °C and $NaHCO_3$ (5 mmol) and MeOH (1.5 mL) were added. After stirring efficiently for 3-5 h the mixture was filtered through a short pad of silica gel. The solution was concentrated under reduced pressure and the diglyceride **3** was purified by chromatography on silica.
In the activated reactions (method B), BF_3•OEt_2 (0.05 mmol) was simply added prior to TFAA.
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Protons of 1,2-diglycerides resonate in 3 groups near 4.2 (CH_2-OC), 5.0 (CH-O), 3.7 (CH_2-OH), and protons of 1,3-diglycerides resonate in 2 groups near 4.0 (CH_2-O), 5.3 (CH-O) (δ ppm in $CDCl_3$ at 200 MHz). The carbon signals are clearly separated: 62.2 (CH_2-OC), 72.2 (CH-OC), 61.5 (CH_2-OH) in 1,2-diglycerides, and 65.1 (CH_2-OC), 68.1 (CH-OH) in 1,3-diglycerides.

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