Chemoenzymatic Synthesis of Enantiopure Structured Ether Lipids

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Ether lipids of the 1-O-alkyl-2,3-diacyl-*sn*-glycerol type are found in medium to high levels in the liver oils of sharks and other species of elasmobranch fish. The most abundant alkyl chains present in the 1-O-alkyl moiety of the 1-O-alkylglycerols are the saturated chains $C_{16:0}$ and $C_{18:0}$ and the monounsaturated chains $C_{16:1}$ and $C_{18:1.}$ The main objective of the current work was to synthesize enantiomerically pure structured ether lipids of the naturally occurring chimyl, batyl and selachyl alcohols ($C_{16:0}$, $C_{18:0}$ and $C_{18:1}$ alkyl chains, respectively) positionally labeled with a pure medium chain fatty acid (MCFA) at the remaining end position and a pure long chain polyunsaturated fatty acid of the n-3 type (EPA or DHA) at the mid position of the glyceryl backbone. The enantiomerically pure chimyl, batyl and selachyl alcohols were prepared by a Williamson ether synthesis using optically pure (*R*)-solketal as a chiral synthon and the corresponding alkyl bromides. Grounded potassium hydroxide was used as a base in the presence of tetrabutylammonium bromide as a phase-transfer catalyst under solvent free conditions. Subsequently the isopropylidene moiety was deprotected under mild acidic aqueous conditions. The immobilized *Candida antarctica* lipase (Novozym 435) showed an excellent regioselectivity toward the end position of all 1-O-alkylglycerols at 0-4 °C using vinyl esters of the MCFA (C_6, C_8, C_{10} and C_{12}). The n-3 fatty acids were subsequently introduced into the remaining mid position highly efficiently using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) as a coupling agent in the presence of dimethylaminopyridine (DMAP). The same methodology was applied to prepare the corresponding positionally labeled ether lipids of the ALM (alkyl-long-medium) type for the opposite 3-O-alkyl-*sn*-glycerol antipodes, starting from optically pure (*S*)-solketal. All products and intermediates were isolated in excellent yields (≥90%) and fully characterized by traditional organic synthesis methods.