SYNTHESIS OF NITRO DERIVATIVES AND FATTY ACID ESTERS OF RICINOLEIC ACID STARTING FROM CASTOR OIL

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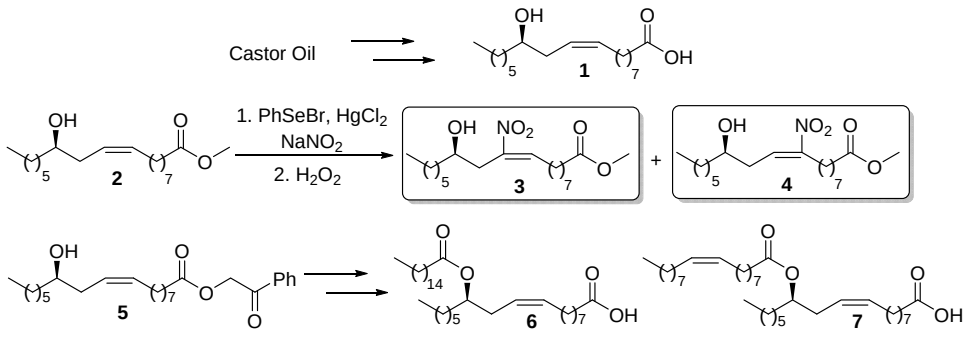
Nitro-fatty acids (NFAs) are endogenously occurring lipid mediators exerting anti-inflammatory effects and acting as anti-oxidants. 10-Nitro-oleic acid (CXA-10) has already entered clinical trials for the treatment of focal segmental glomerulosclerosis [1]. Anti-tumorigenic effects of NFAs (9- and 10-nitro oleic acid) on colorectal cancer cells in cell culture-based experiments and in a murine xenograft model have been reported [2]. On the other hand, Fatty Acid esters of Hydroxy Fatty Acids (FAHFAs) have been recently reported as a novel class of endogenous lipids presenting anti-diabetic and anti-inflammatory activity [3]. The aim of our work was the synthesis of novel ricinoleic acid (RA, 12-R-hydroxyoleic acid) derivatives to evaluate their biological properties. RA can be easily isolated from castor oil, because it is the predominant fatty acid (up to 85–90%) to the existent triglycerides. In this work, we describe the synthesis of 9- and 10-nitro ricinoleic acid derivatives, as well as FAHFAs based on RA, using castor oil as the starting material. Methanolysis of castor oil, followed by saponification, provides RA **1**, in 50% yield. Castor oil was treated with MeOH/c.H_2SO_4 and the resulting methyl ricinoleate **2** subsequently reacted with PhSeBr, $HgCl_2$, $NaNO_2$ and then with H_2O_2 to afford a mixture of 9- and 10-nitro regioisomers **3** and **4**, which were separated by column chromatography. 12-Palmitic Acid ester of Ricinoleic Acid (**6**, 12-PARA) as well as the corresponding oleic acid derivative (**7**, 12-OARA) were synthesized after protecting the carboxyl group of RA with phenacyl bromide, coupling with palmitic acid or oleic acid, and finally deprotection with TBAF in THF. 9- and 10-nitro-oleic acid derivatives, as well as the corresponding methyl esters, have been also synthesized by slight modification of the published procedures [4] in order to compare their cytotoxic activities with those of the novel nitro-ricinoleic acid derivatives. The evaluation of the biological properties of these compounds is in progress.



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[4] M. Gorczynski et al, *Org. Lett.* **2006**, 8, 11, 2306.