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Synthesis of a Radioactive Photoaffinity Arachidonic Acid Analog

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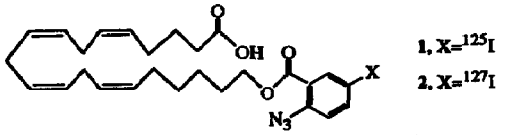
Abstract: **A novel photoaffinity probe based on arachidonic acid was synthesized by coupling 20-hydroxyarachidonic acid and 2-azido-5-iodobenzoic acid. The key epoxide required for the formation of 20-hydroxyarachidonic acid was obtained using a new mild and safe method.**

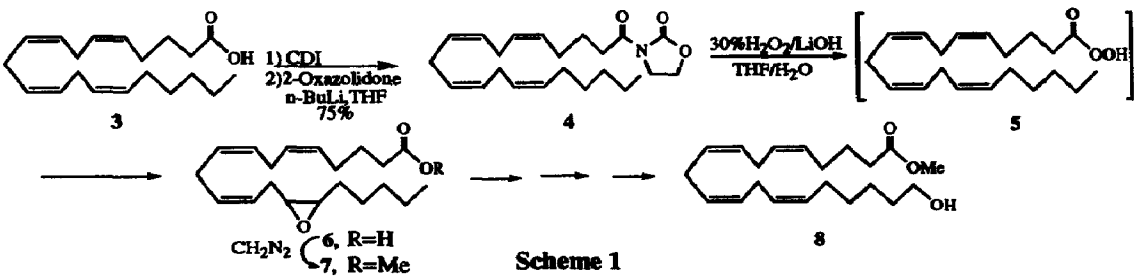
Arachidonic acid is the endogeneous substrate of both lipoxygenase and cycloxygenase pathways, which are involved in asthma, pain and inflammation.[1] The studies of these pathways undertaken in our laboratories required the use or a radiolabelled photoaffinity arachidonic acid derivative. Compound **1** was designed as a potential probe because it is desirable to have the moiety bearing both the azido and the iodo group as far away as possible from the double bonds and the carboxyl group, since these are the recognition elements of arachidonic acid for a variety of proteins. The compound **1** could be readily prepared by coupling 20-hydroxyarachidonic acid and 2-azido-5-iodobenzoic acid. This benzoic acid derivative can be used as a general synthon for use in photoaffinity labelling by coupling it to other bioactive molecules.



1, X=^{125}I
2, X=^{127}I

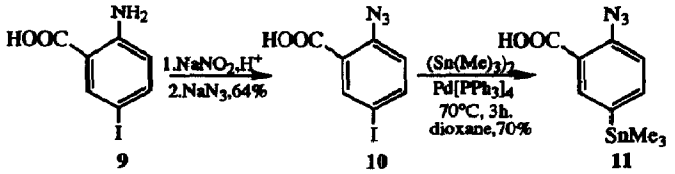
The preparation of 20-hydroxyarachidonic acid has been described.[2] Unfortunately, the formation of the key 14,15-epoxide of arachidonic acid **6** requires handling hazardous 90% H_2O_2 in ether.[3] We would like to report a milder and safer method for formation of the intermediate peracid **5** as well as the synthesis of the probe **1**.

Arachidonic acid was treated with carbonyl diimidazole (**Scheme 1**) followed by the lithium salt of 2-oxazolidone, to give **4** in 75% yield. This compound was then treated with lithium hydroxide and 30% aqueous hydrogen peroxide[4] followed by aqueous work up to give the peracid **5**. This species rearranges over 12h in CH_2Cl_2 to give the epoxide **6**. Upon treatment with diazomethane, the resulting methyl ester **7**, obtained in 70% overall yield, was converted to the desired methyl 20-hydroxyarachidonate **8** as previously reported.[2]



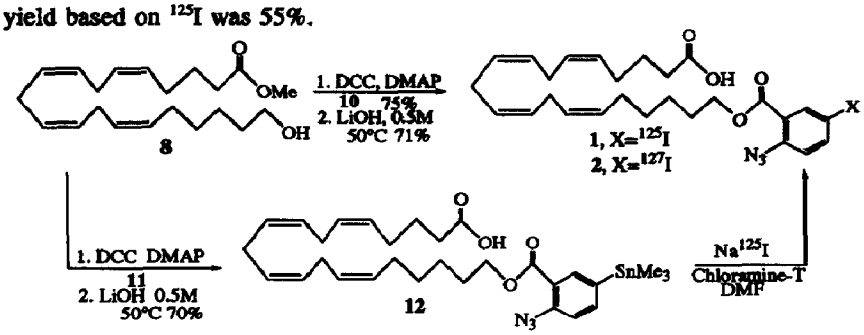
Scheme 1

The aromatic portion of the molecule **1**, containing the photoactivatable azido group and the iodo label was then prepared. We elected to prepare 2-azido-5-iodobenzoic acid,**10**, through a diazonium ion from the commercially available 2-amino-5-iodobenzoic acid (**Scheme 2**). An efficient way for introducing radioactive iodine is through the oxidation of a stannyl derivative with radioactive sodium iodide and chloramine-T.[5] The stannyl compound **11** was prepared via palladium catalyzed stannylation of the iodide **10**.[6]



Scheme 2

The coupling of the two fragments **8** and **10** afforded, after selective hydrolysis, product **2** (**Scheme 3**). Under the same coupling conditions, the stannyl derivative **11** and the alcohol **8** gave **12**. Compound **12** in DMF was iodinated with [^{125}I] sodium iodide(0.01M/pH7) in the presence of chloramine-T(0.01M/DMF). After 30 minutes at room temperature, the reaction mixture was quenched with sodium sulfite and compound **1** was purified directly by RP-HPLC (20% 25 mM aqueous ammonium acetate, 80% methanol, Novapack C_{18}). The radiochemical yield based on ^{125}I was 55%.



Scheme 3

We have described the synthesis of a novel radioactive photoaffinity probe based on arachidonic acid. The successful use of **1** in the labelling of proteins involved in the arachidonic cascade has been reported.[7]

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