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A SIMPLE PROCESS FOR THE PURIFICATION OF ARACHIDONIC ACID

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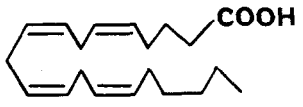
Summary: Pure arachidonic acid (1) and docosahexanoic acid (3) are available by a two-step purification method from commercial 50% acids with high efficiency.

Arachidonic acid (1) is an important starting material for biochemical studies and for the synthesis of eicosanoids such as leukotrienes and inhibitors of leukotriene biosynthesis.[1] The high price of commercially available pure arachidonic acid has prompted the development of methods for the purification of impure (50%) but less expensive commercial material. Previous methods[2] have involved several laborious and expensive steps including chromatographic purification on silver nitrate impregnated silica gel.

The iodolactonization of arachidonic acid to form 2[3] was recognized as a valuable step for purification since arachidonic acid is the only fatty acid present in the impure commercial mixture of acids that is capable of forming iodolactone. The next element required for a purification process, regeneration of arachidonic acid from 2, could not be carried out in the normal way, i.e., reaction with metals such as zinc or magnesium, since mixtures of 1 and the 5-E-isomer were formed under a wide variety of reductive conditions (ratio of Z/E 3 : 1 to 2 : 1). A multistep sequence, iodolactone ⟶ 5,6-epoxide ⟶ 5,6-episulfide ⟶ 1,[4] though successful, was time-consuming. A much simpler and effective one-step method was developed as follows.

Reaction of 2 with chlorotrimethylsilane and sodium iodide in acetonitrile at 23°, followed by aqueous workup to effect hydrolysis of the intermediate trimethylsilyl ester afforded pure 1[4] in 97% yield.[5] These elimination conditions were devised on the speculation that generated in situ iodotrimethylsilane could coordinate with the lactone function, activating the system for I^- promoted attack to form the arachidonic acid trimethylsilyl ester by a concerted, antiperiplanar elimination. The same elimination conditions allowed the stereospecific formation of docosahexaenoic acid (3) from the corresponding iodo-γ-lactone 4[4] in 95% yield.[6]

In a typical preparation, a solution of 2 (4.686 g, 10.9 mmol) in 75 ml of dry acetonitrile was added to a suspension of dry sodium iodide (8.161 g, 54.4 mmol) in 50 ml of acetonitrile. Following the complete solution of the sodium iodide, chlorotrimethylsilane (2.76 ml, 21.8 mmol) was added and the mixture was stirred for 1 h at 23°. Water (175 ml) and sodium thiosulfate (20 g) were added and the mixture was extracted 4 x 50 ml with 25% dichloromethane in hexane. The combined extracts



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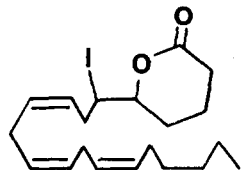

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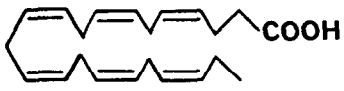

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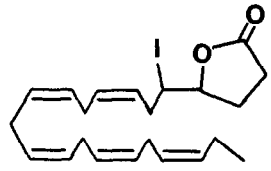

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were washed with water (4 x 50 ml), brine (2 x 50 ml), dried ($MgSO_4$) and evaporated to give 3.206 g (97%) of pure 1.[7]

References and Notes

1. (a) E. J. Corey, A. E. Barton and D. A. Clark, J. Am. Chem. Soc., 102, 4278 (1980); (b) E. J. Corey and A. E. Barton, Tetrahedron Letters, 23, 2351 (1982).
2. F. A. Dudley and R. E. Anderson, Lipids, 10, 113 (1975).
3. (a) E. J. Corey, J. O. Albright, A. E. Barton, and S. Hashimoto, J. Am. Chem. Soc., 102, 1435 (1980); (b) E. J. Corey and S. Hashimoto, Tetrahedron Letters, 22, 299 (1981). 50% arachidonic acid was obtained from Nu Chek Prep, Inc.
4. E. J. Corey, C. Shih and J. R. Cashman, Proc. Natl. Acad. Sci. USA, 80, 3581 (1983).
5. No (E)-olefin formation could be detected by 270 MHz PMR or chromatographic analysis of the product.
6. In situ-generated iodotrimethylsilane has also been employed for the conversion of epoxides to olefins; see R. Caputo, L. Mangoni, O. Neri and G. Palumbo, Tetrahedron Letters, 22, 3551 (1981).

7. This work was assisted financially by a grant from the National Institutes of Health.

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