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Total Synthesis of the Naturally Occurring Furanoid Fatty Acid, F_5

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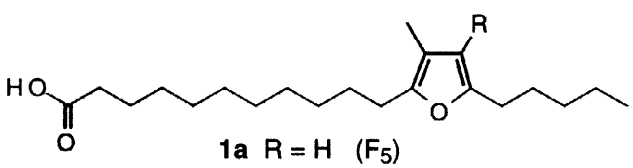
Abstract: *The furanoid fatty acid F_5 has been synthesized using a mercury(II) catalyzed isomerization of 2-(1,2-oxiranylcyclododecyl)-3-nonyn-2-ol.*

The furanoid fatty acids (F-acids), originally isolated from *Exocarpus* seed oil,[1] are abundant in fish lipids[2] and are also found in marine sponges,[3] latex,[4] and a variety of foodstuffs including butter.[5] F-acids from plants are generally 2,5-disubstituted furans, but those from marine sources may contain a tri- or tetra-substituted furan, *e.g.* **1a** (F_5), **1b** (F_6), and their numerous homologues.[6] Although the biological function of the F-acids remains to be elucidated,[7] evidence suggests that the urofuran acids found in human beings are derived by metabolism of F-acids.[8] The high levels of F-acids in liver and testes lipids of fish, the preferential esterification of cholesterol by F-acids, and their implication in reproduction[2a,c] are further reasons for improving accessibility to F-acids through synthesis.



1a R = H (F_5)
1b R = Me (F_6)

Efficient routes to 2,3,5- and 2,3,4,5-substituted furans are few, modification of lesser substituted furans proceeding in several low-yielding steps.[9] Thus, the methyl ester of **1a** (F_5) was obtained in less than 3% overall yield from the furan precursor 3-methyl-2-furoate, and contaminated with methyl undecanoate.[9] We here report a total synthesis of **1a** (F_5) starting from commercially available cycloundecanone (**2**).

Addition of 1-heptynyllithium to cycloundecanone (**2**) afforded 1-(1-heptynyl)cyclododecan-1-ol which was converted into 1-acetyl-1-cyclododecanone (**3**) by Rupe rearrangement.[10] Addition of *n*-heptynyllithium gave the tertiary allylic alcohol (without

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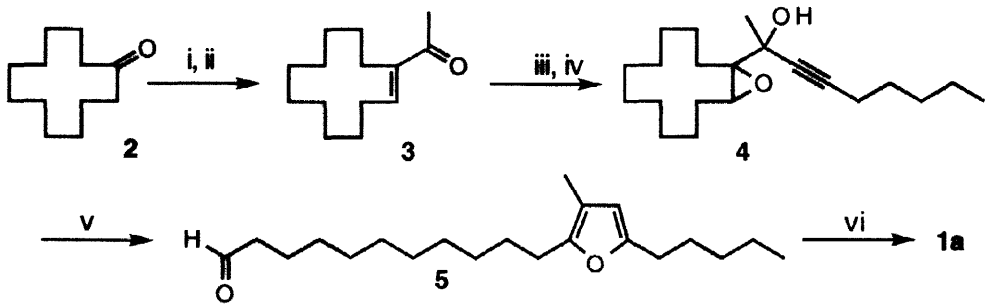

Scheme 1. *Reagents and conditions*: i, lithium acetylide (1.1 equiv. in THF), 25 °C, 1.5 h (75%) ii, aqueous HCOOH (90%), reflux 3 h (64%) iii, heptynyllithium (1.1 eq.), 20 °C, 4 h (68%) iv, aqueous *tert*-butyl hydroperoxide (2.0 eq., 70%), cat. $VO(acac)_2$, 20 °C, 4 h (69%) v, 0.32 mol% Hg(II) in aqueous 1.5 mM H_2SO_4 (88%) vi, pyridinium dichromate (5.0 eq.), 20 °C, 6 h (65%).

significant 1,4-addition) which on epoxidation[10] gave **4** as a 4:1 mixture of diastereoisomers. This mixture of **4** was treated with 0.32 mol% of Hg(II) in aqueous 1.5 mM H_2SO_4,[11,12] resulting in catalytic isomerization to the furan **5**, the sole product isolated (88%). The aldehydic group of **5** was oxidized with pyridinium dichromate to deliver **1a** (F_5) (65%).

Advantages of the present route include assembly of the total carbon framework prior to formation of the furan ring, tolerance of the catalytic isomerization by sensitive functionality, and the use of mild conditions throughout. The methodology is adaptable to the synthesis of a variety of furanoid natural products including other fatty acids and the calicogorins, defence allomones of gorgonian coral.

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12. Alcohol **4** (4:1 *syn:anti* mixture) (100 mg, 3.13 mmol) in propanone (30 mL) was treated for 10 min at 20 °C with 0.1 mL of a 0.1 M solution of Hg(II), obtained by dissolving *yellow* HgO in aqueous H_2SO_4 (2.5% v/v). Chromatography on silica (ethyl acetate:petroleum ether, 1:9) gave **1a** as an oil (88 mg); ^1H NMR ($CDCl_3$) δ_H 5.73 (1H, s), 2.50 (4H, m), 2.34 (2H, t, J = 8 Hz), 1.89 (3H, s), 1.58 (6H, m), 1.29 (16H, m), 0.89 (3H, t, J = 8 Hz). Anal. Calcd for $C_{21}H_{26}O_3$ 336.2664, found 336.2657.