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Preparation of 11-Substituted Linoleic Acids[1]

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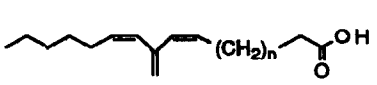
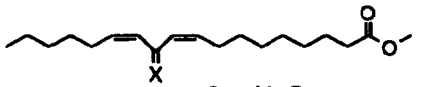
Key Words: irreversible inactivators; linoleic; 15-lipoxygenase; periodinane; active manganese dioxide

Abstract: A novel, direct route to 11-substituted linoleic acids was devised. These include **1b**, a homolog of an irreversible inhibitor of soybean 15-lipoxygenase, as well as esters **2a** and **2b**, which were recently isolated from a *Lithothamnion corallioides* preparation.

Pursuant to ongoing studies of 15-lipoxygenase enzymes,[2] we recently undertook the preparation of compounds of type **1**. One member of this series, 12-methylidene-10(Z),13(Z)-nonadecadienoic acid **1a**,[3] is reported to irreversibly inactivate soybean lipoxygenase. The published synthesis of **1a** is remarkable for its brevity and directness; however, it contains two features which limited its suitability to our aims. Firstly, HPLC purification of a penultimate compound is required; this limits throughput significantly. Secondly, the direct nature of the synthesis precludes a more general exploration of 11-substituted linoleic acids. Such compounds, specifically 11-hydroxy- and 11-oxolinoleic acids, were recently reported[4] (isolated as methyl esters **2a, b**) as enzymatic products derived from a preparation of the alga *Lithothamnion corallioides*.



1a: n=7
1b: n=6

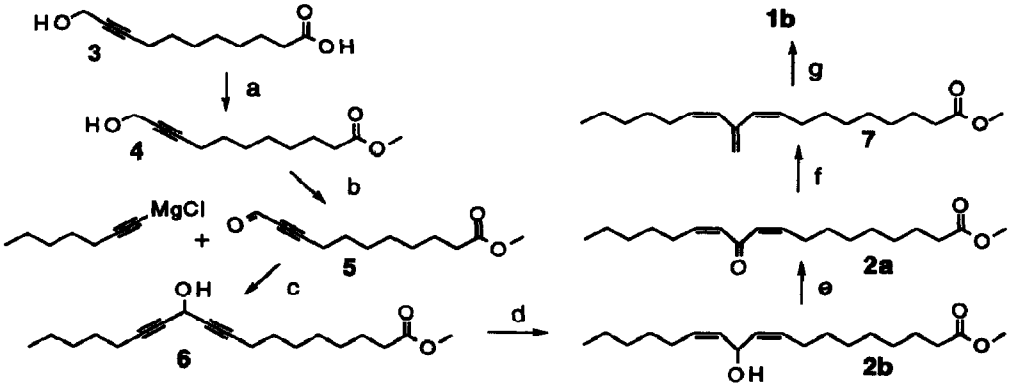


2a: X=O
2b: X=H; OH

Our aim became to prepare a homolog of **1a**, namely 11-methylidene-9(Z),12(Z)-octadecadienoic acid **1b**, possessing the same carbon backbone as a natural 15-LO substrate, linoleic acid. The preparative route described herein allows making quantities of **1b** in a completely stereospecific manner.

The starting point for our synthetic strategy is the C_{11} acid **3**,[5] which was esterified to **4** under modified Fischer conditions (94%).[6] Oxidation of **4** with Dess-Martin periodinane[7] (96%) afforded the acetylenic aldehyde **5**, which reacted smoothly with 1-heptynylmagnesium chloride (84%) to yield C_{18} ester **6**. Lindlar reduction[8] to **2b** succeeded when the catalyst was pretreated with hydrogen, affording **2b** in 88% yield. Attempted periodinane reaction of **2b** led to decomposition. However, oxidation was cleanly effected with neutral active manganese dioxide[9] (85%) to yield **2a** as a stable oil (UV, MS spectra match lit.).[4] Wittig reaction[10] followed by chromatography (silica, 12:1 hexane: ether) led to recovery of 39% of **7**, chemically and isomerically pure by ^1H and ^{13}C NMR. LiOH saponification[2] cleanly afforded **1b** as a colorless oil.[11]

Scheme: Preparation of Acid **1b**



Reagents and Conditions: a) 50 equiv CH_3OH, 1.5 equiv $SOCl_2$, rt,16 h. b) 1.3 equiv periodinane, CH_2Cl_2, rt,1 h. c) 1-heptyne, 3M MeMgCl in THF, 65°C,3 h; then **5**, THF, -78°C, 1 h. d) Pd/Pb on $CaCO_3$ (Aldrich), 10% pyridine/CH_3OH, rt, H_2 (atm), 3 h. e) MnO_2 (1 g/mmol), CH_2Cl_2, rt, 45 min. f) THF, -78°C, 1.0 eq Ph_3PCH_3Br, 1 equiv n-BuLi in hexane; then 1 equiv **2a**, -78°→ 0°C, 3 min. g) LiOH, 1:2 H_2O/THF, rt, 16 h.

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References and Notes

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11. All compounds were characterized by high-field ^1H NMR, EIMS, and for **2a**, **2b** and **7**, elemental analysis.

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