# Synthesis of Dimethyl-Substituted $C_{18}$ Furanoid Fatty Ester

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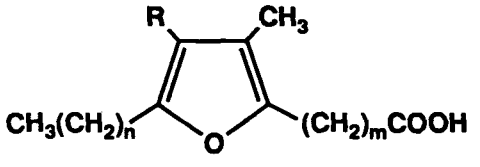
**Reaction of a $C_{18}$ furanoic fatty acid with dimethyl dicarboxylate (DMAD) furnished the corresponding bicyclo Diels-Alder adduct, which was partially hydrogenated over Pd/$BaSO_4$. Heat treatment (160–180°C) of the partially hydrogenated product caused a retro-Diels-Alder reaction to yield a furanoid fatty acid derivative containing methoxycarbonyl ($COOCH_3$) substituents at the 3- and 4-positions of the furan nucleus. Reduction of the $COOCH_3$ substituents with $LiBH_4$ gave the corresponding $CH_2OH$-substituted furanoid fatty acid. Hydrogenation of the latter over Pd/C furnished the desired dimethyl-substituted furanoid acid derivative (overall yield 60%). The spectroscopic properties of the intermediates and product are reported.**

KEY WORDS: Dimethyl substituted, fatty acid, furanoid, physical properties, synthesis.

Furanoid fatty acids (**I**) containing methyl substituents at the 3- and/or 4-positions of the furan system have been found in the lipid extracts of a number of fish species (Fig. 1) (1,2). In the latex of the rubber plant *(Hevea brasiliensis)*, the major component (>90%) of the triglyceride fraction consists of 10,13-epoxy-11-methyl-10,12-octadecadienoic acid (3). Furanoid fatty acids have been identified as minor components in a large variety of common plant species (4). This class of heteroaromatic fatty acids has also been found to occur in the lipid extracts of soft corals (5), crayfish (6), amphibians and reptiles (7), liver of cattle (8) and in the phospholipid fraction of human and bovine blood plasma (9,10). The biosynthesis route to the natural furanoid acids remains undetermined and the role of these unusual fatty acids is still unclear.

We have reported the synthesis of some $C_{18}$ furanoid fatty esters containing a methyl substituent at the 3- and/or 4-positions of the furan nucleus from derivatives of methyl ricinoleate (11,12). The preparations of 3,4-dimethyl-substituted $C_{18}$ and $C_{20}$ furanoid fatty esters have also been reported (13). A method for the incorporation of a methyl group into the 3- and/or 4-positions of the furan nucleus of a $C_{18}$ furanoid fatty ester *via* a malonic acid derivative has recently been developed (14). In this paper we present a facile and high-yield synthesis to introduce methyl groups into the 3- and 4-positions of the furan nucleus by way of a Diels-Alder cycloaddition reaction (Fig. 2).




I

R = H, $CH_3$; $n = 2$ or 4; $m = 8$, 10 or 12

FIG. 1. Long-chain furanoid fatty acids in fish.

## MATERIALS AND METHODS

*Instruments.* Thin-layer chromatographic (TLC) analysis was performed on microscope glass plates coated with silica gel (*ca.* 0.1 mm thickness) and a mixture of petroleum ether (b.p. 40–60°C):diethyl ether was used as the developer [PE30 denotes a mixture of petroleum ether:diethyl ether (70:30, v/v) where the numeral stands for the percentage of ether in the developer]. Column chromatographic purification was carried out on silica gel, and a mixture of petroleum ether and diethyl ether was used as the eluant. Infrared (IR) spectra were obtained on a Perkin-Elmer (Perkin-Elmer, Norwalk, CT) model 577 spectrophotometer, and nuclear magnetic resonance (NMR) spectra were performed on a JEOL (JEOL Ltd., Tokyo, Japan) GSX-270 (270 MHz) Fourier transform spectrometer at 270.05 MHz for protons and at 67.8 MHz for carbon observation. Chemical shifts (ppm) are reported relative to $Me_4Si$ as internal standard. Connectivities in the $^1H$-$^{13}C$ NMR spectra were established at 270.05 MHz by using a combination of spin-spin decoupling, COSY and double quantum filter experiments. Carbon atom types were established in $^{13}C$ NMR by a combination of broad-band proton decoupling and DEPT experiments. 9,12-Epoxy-9,11-octadecadienoic acid was prepared from ricinoleic acid as described elsewhere (15). Dimethyl acetylenedicarboxylate and lithium borohydride were purchased from Aldrich Chemical Co. (Milwaukee, WI). All solvents were distilled before use. Results of the elemental analyses of all products were consistent with the structure of the compounds.

*Reaction of 9,12-epoxy-9,11-octadecadienoic acid with dimethyl acetylenedicarboxylate.* A mixture of 9,12-epoxy-9,11-octadecadienoic acid (**II**, 3.0 g, 10.2 mmol), dimethyl acetylenedicarboxylate (1.8 g, 12.7 mmol) and benzene (30 mL) was refluxed for 5 hr. The solvent was evaporated under reduced pressure and silica (60 g) column chromatographic separation of the residue with a mixture of PE70 as the eluant furnished compound **III** (4.2 g, 93%) as an oil.

*Hydrogenation of compound* **III.** A mixture of compound **III** (2.0 g, 4.6 mmol), palladium on barium sulfate (10%, 100 mg) and *n*-hexane (30 mL) was stirred in a hydrogen atmosphere at room temperature at 780 mm Hg pressure for 15 min. The mixture was filtered, and the solvent was evaporated under reduced pressure to give compound **IV** (2.0 g, 99%) as an oil.

*Preparation of 9,12-epoxy-10,11-dimethoxycarbonyl-9,11-octadecadienoic acid* (**V**). Compound **IV** (1.5 g, 3.4 mmol) was heated at 160–180°C for 3 hr under nitrogen. Silica column chromatography (60 g silica with PE60 as eluant) of the residue gave compound **V** (1.2 g, 86%) as an oil.

*Lithium borohydride reduction of compound* **V.** A mixture of compound **V** (1.0 g, 2.4 mmol) and tetrahydrofuran

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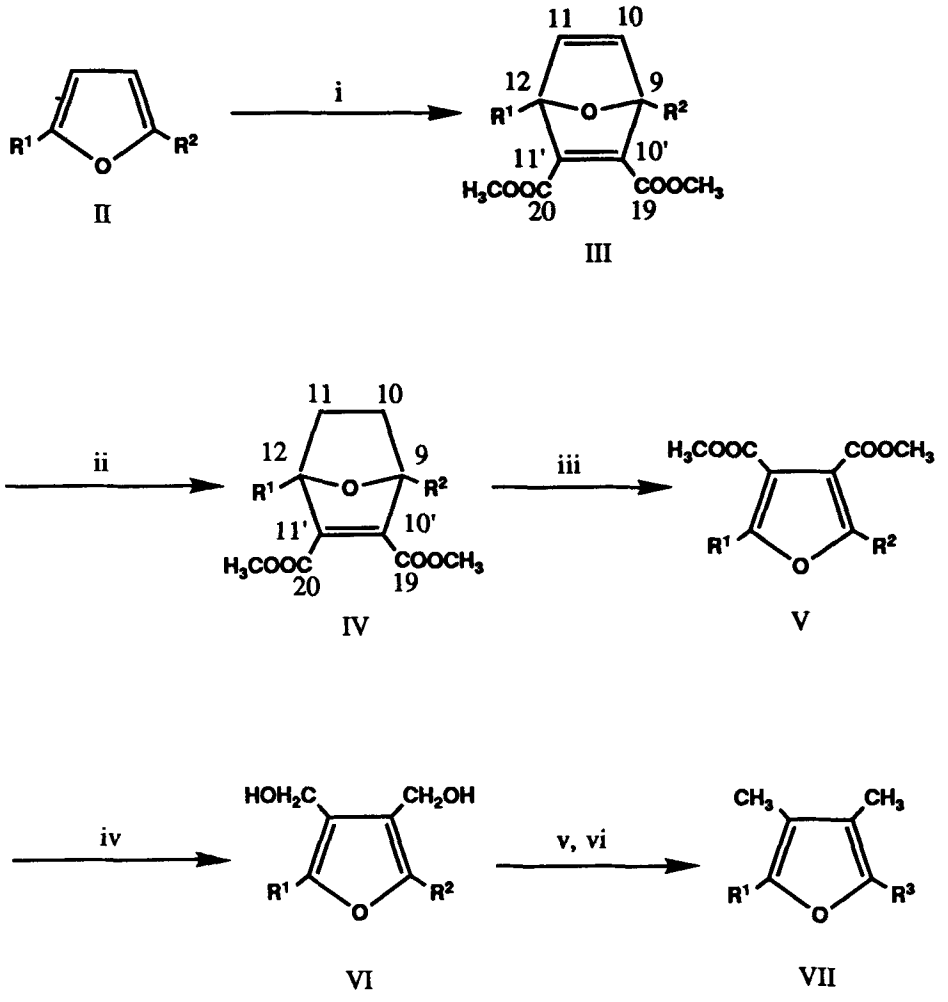


FIG. 2. Synthesis of dimethyl-substituted $C_{18}$ furanoid fatty ester.

(THF) (20 mL) was stirred at 0°C under nitrogen. Lithium borohydride in THF (2.0 M, 1.5 mL) was added with a syringe. The reaction mixture was allowed to stir at room temperature for 3 hr. The reaction mixture was cooled in an ice bath, and a mixture of THF:water (1:1, v/v, 10 mL) was added. Dilute HCl (1M, 20 mL) was then added, and the reaction mixture was extracted with diethyl ether (3 × 20 mL). The organic extract was washed with brine (20 mL), and was dried over anhydrous sodium sulfate. The extract was filtered, and the solvent was evaporated to give compound **VI** (0.81 g, 95%) as an oil.

*Preparation of methyl 9,12-epoxy-10,11-dimethyl-9,11-octadecadienoate* (**VII**). A mixture of compound **VI** (1.0 g, 2.8 mmol), palladium on carbon (10%, 100 mg) and absolute ethanol (20 mL) was stirred in an atmosphere of hydrogen at room temperature at 780 mm Hg pressure for 30 min. The reaction mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was refluxed with methanol (10 mL) and borontrifluoride-methanol complex (10%, w/w, 5 mL) for 15 min. Brine (20 mL) was added, and the reaction mixture was extracted with petroleum ether (3 × 20 mL). The organic extract was washed with water (20 mL) and was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give compound **VII** (0.72 g, 76%) as an oil.

## RESULTS AND DISCUSSION

The Diels-Alder cycloadduct formation between 9,12-epoxy-9,11-octadecadienoic acid with dimethyl acetylenedicarboxylate (DMAD) was accomplished in high yield (93%) (16). In the $^1H$ NMR analysis of the bicyclo adduct (**III**), the presence of the ester function derived from DMAD was confirmed by the signals at $\delta$ 3.78 (*s*, 6H). The shift of the ethylenic protons of the bicyclo system appeared at $\delta$ 6.90. In the $^{13}C$ NMR analysis of compound **III**, the oxygen bridge linking the C-9 with C-12 carbon atoms caused these nuclei to shift downfield to 95.9 ppm. The shift of the unsaturated carbon atoms, originating from DMAD and substituted with $COOCH_3$ groups appeared at 154.7, 155.0 ppm. The shift of the remaining unsaturated carbon atoms appeared at 146.3 (2C) ppm. The signals for the carbonyl carbons of the $COOCH_3$ groups were shifted to 164.7, 164.8 ppm.

Hydrogenation of compound **III** over palladium on barium sulfate allowed the less-hindered ethylenic bond of the bicyclo system to be saturated in 15 min to yield compound **IV** in quantitative yield (99%) without further saturation of the remaining ethylenic bond (17). However, prolonged hydrogenation (2 hrs) eliminated the ethylenic bonds of compound **III** completely. The methyl ester function in compound **IV** was characterized from the peak at 1745 $cm^{-1}$ in the infrared spectrum and by the appearance of a singlet at $\delta$ 3.79 ($COOC\underline{H}_3$) in the $^1H$ NMR spectrum. In the $^{13}C$ NMR analysis, the unsaturated carbon nuclei were shifted to 144.8, 145.1 ppm and the shift of the ring methylene carbon atoms appeared at 32.4 ppm.

The partially hydrogenated adduct (**IV**) was thermally unstable when heated at 160–180°C (16). This retro-Diels-Alder reaction furnished a fully tetrasubstituted furan derivative (**V**) (86% yield), containing methyl ester groups at the 3- and 4-positions of the furan nucleus. The $^1H$ NMR spectral analysis confirmed the presence of the methyl ester groups by the signals at $\delta$ 3.82(*s*) for the shift of the methyl protons of these groups. The shifts of the carbon nuclei of the furan ring appeared at 113.1 (C-10, C-11), 159.4 (C-12) and 159.6 (C-9) ppm, and those of the carbonyl carbon atom of the methyl ester groups appeared at 164.1 ppm.

Reduction of the methyl ester groups in compound **V** was readily achieved by treatment of the substrate with lithium borohydride in THF to give compound **VI** in quantitative yield. The absorption peak for the hydroxy function of the $CH_2OH$ substituent in compound **VI** coalesced with the O–H stretching vibration of the carboxylic acid function in the infrared spectrum (3400, *br* O–H). However, the $CH_2OH$ substituent was readily distinguished by $^1H$ NMR analysis, where the shift of the methylene protons of the $CH_2OH$ group appeared as a singlet at $\delta$ 4.44 (*s*, 4H). The shift of the hydroxy protons appeared at $\delta$ 2.0 ($D_2O$ exchangeable). In the $^{13}C$ NMR analysis of compound **VI**, the shift of the methylene carbons of the $CH_2OH$ groups were further confirmed as they appeared at 55.1 (2C) ppm. The carbon nuclei of the furan system were shifted to 119.6 (C-10, C-11) and 152.2 (C-9, C-12) ppm.

Transformation of the $CH_2OH$ substituents to a methyl group was achieved by catalytic hydrogenation over 10% palladium on carbon. This novel reduction process was first observed in the preparation of a methyl-substituted furanoid fatty ester derivative *via* a malonic acid function (14). Thus, catalytic hydrogenation of compound **VI** gave the dimethyl substituted furanoid acid, which was esterified to the methyl 9,12-epoxy-10,11-dimethyl-9,11-octadecadienoate (**VII**, 76%) for ease of purification and identification purposes.

The methyl substituents of the furan ring of compound **VII** were characterized by the signal at $\delta$ 1.82 (*s*, 6H, furan-$C\underline{H}_3$) in the $^1H$ NMR spectrum. The $^{13}C$ NMR spectral analysis confirmed these methyl substituents, which appeared upfield at 8.3 (2C, furan-$\underline{C}H_3$) ppm. The shifts of the carbon nuclei of the furan ring appeared at 114.5 (C-10, C-11) and 148.5 (C-9, C-12).

From these results, it can be concluded that the Diels-Alder approach is a high-yielding and facile method for the synthesis of dimethyl-substituted furanoid fatty acid derivatives with an overall yield of 60% from a readily available disubstituted furanoid fatty acid substrate. This method also provides a ready means to substitute the 3- and 4-positions of the furan nucleus with other organic functional groups other than methyl groups.

## ACKNOWLEDGMENTS

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