Novel halo-oxo-allenic fatty ester derivatives from epoxidized methyl santalbate (methyl trans-11-octadecen-9-ynoate)


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Abstract

Methyl santalbate (methyl trans-11-octadecen-9-ynoate) from Sandal wood seed oil, Santalum album) was epoxidized to methyl trans-11,12-epoxy-octadec-9-ynoate (1). Treatment of compound 1 with tetrabutylammonium dihydrogen trifluoride, and boron trifluoride etherate gave the corresponding anti- (2a) (57%) and syn- (2b) (35%) fluorohydrin derivatives, respectively. These reactions were regio- and stereoselective in nature. The structures of the anti- and syn- isomers were confirmed by NMR spectroscopy. Ring opening of the epoxy system of compound 1 with lithium chloride gave the anti-chlorohydrin derivative (3) (89%). Oxidation of either compound 2a or 2b gave the same fluoro-keto acetylenic fatty ester (4) (75%), and compound 3 on chromic acid oxidation yielded the corresponding chloro-keto acetylene (5) (73%). Isomerization of compounds 4 and 5 with potassium carbonate in dichloromethane furnished the requisite fluoro-allenic (6) (63%, methyl 11-fluoro-12-oxo-9,10-octadecadienoate) and chloro-allenic (7) (80%, methyl 11-chloro-12-oxo-9,10-octadecadienoate) C18 fatty esters. All products were confirmed by a combination of spectrometric and spectroscopic techniques.

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1. Introduction

Naturally occurring halogenated fatty acids are rare, as relatively few of such fatty acids have been reported in the chemical literature. Fatty acids containing an α-fluoro group (viz. α-fluoro-16:0, 16:1, 18:0, 18:1, 18:2, 20:0, and 20:1) were identified in the seed oil of Dichapetalum toxicarium (Hamilton and Harper, 1997; Christie et al., 1998). Fatty acids containing chloro and bromo groups were found in marine organisms (Mu et al., 1997; Scheuer, 1978). For example, chlorohydrins of C16 and C18 fatty acids were reported in the lipoid extract of a jelly fish (White and Hager, 1977). Brominated acetylenic fatty acids were isolated from species of the marine sponges Xestospongia muta and Xestospongia testudinaria (Schmitz and Gopichand, 1978; Quinn and Tucker, 1985).
Chlorination and bromination of the olefinic bonds in common unsaturated fatty acids are readily achieved. Brominated vegetable oils were once used in the soft drink industry to create a "pulpy" (sediment) appearance in an orange drink (Mohamed et al., 1980). Such substances are now banned as food additives, as they appear to be toxic or even carcinogenic. Reaction of linoleic acid and chlorine water gave a mixture of tetrachlorostearic acid, dichloro, and trichlorohydrins of linoleic acid (McKague and Reeve, 1991). Chlorohydrins of fatty acids were also readily obtained by reaction of the corresponding epoxy fatty acid with anhydrous HCl in diethyl ether (Swern, 1948). Dehydrochlorination reaction of chlorohydrins of fatty acids were also studied (Ketola, 1973; Pihlaja et al., 1976). Of interest was the oxidation reaction of chlorohydrins of a C₁₈ fatty acid producing some chloro-ketone derivatives, which on dechlorination with NaOH resulted in the production of a mixture of half esters of dicarboxylic acids (Ketola and Leskinen, 1985). Many iodinated fatty acids were prepared by Osman et al. (Khan et al., 1988). However, the most useful of reactions of unsaturated fatty acids with iodine appeared to be the iodolactone formation of fatty acids containing a double bond at C-5/C-6 of the alkyl chain. This iodolactonization reaction has allowed many important natural poly-unsaturated fatty acids (such as eicosapentaenoic acid, EPA and docosahexaenoic acid, DHA) to be isolated from fish oils in gram quantities (Corey and Wright, 1984; Gaiday et al., 1991).

Nature does not produce many allenic fatty acids. Laballenic acid (5,6-octadecadienoic acid) was isolated from the seed oil of Leonotis nepetaelofilia (Hagemann et al., 1967) and lamenallenic acid [(−)-octadeca-5,6-trans-16-trienoic acid] was found in the seed oil of Lamium purpureum (Mikolajczak et al., 1967). Some medium chain polyunsaturated allenic fatty acids with potential anti-microbial properties were identified in the lipid extracts of a number of basidomycete moulds. Mycomycin (3-trans-5-cis-7,8-tridecatraeene-10,12-diynoic acid), nemotinic acid (4-hydroxy-5,6-undecadiene-8,10-diynoic acid), and 3,4-nonadiene-6,8-diynoic acid were isolated from the culture media of Norcardia acidophyllus (Celmer and Solomons, 1952), Poria sp. (Kavanagh et al., 1949; Ancel et al., 1950; Bullock and Leadbeater, 1956), and Aluerodiscus roseus (Cambie et al., 1963), respectively. Recently, two new bromoallenic fatty acids have been reported in lichens: (12E,15S,18S)-15-hydroxy-18-bromo-12,16,17-octadecatrienoic acid and (13Z,15R,18S)-15-hydroxy-18-bromo-13,16,17-octadecatrienoic acid (Dembiski, 2003). Lie Ken Jie and Wong (1992) synthesized the positional isomers of allenic 18:2 fatty esters.

Santalic acid contains a unique conjugated enyne system in the alkyl chain, which could be successfully exploited by Biermann et al. (2000a) to obtain 12-chloro-9-(1-oxoheptyl)-9,10-octadecadienoate by Friedel–Crafts acylation and methyl 9-isopropyl-9,10-octadecadienoate by Friedel–Crafts alkylation.

This paper reports the preparation of novel fluoro-oxo-allenic and chloro-oxo-allenic fatty acid derivatives, which is part of our on-going goals in the development in lipid chemistry to utilize renewable plant resources to produce potentially useful lipid molecules for the pharmaceutical and oleochemical industries (Biermann et al., 2000b).

2. Materials and methods

Column chromatographic separation was performed using silica gel (type 60, 70–230 mesh, Merck, Darmstadt, Germany) as the adsorbent using gradient elution with mixtures of n-hexane/diethyl ether as the mobile phase. Thin layer chromatographic analysis was carried out on pre-coated silica plates (Merck 1.05715, silica gel 60 F₂₅₄, layer 0.1 mm thick, Darmstadt, Germany) using various mixtures of n-hexane and diethyl ether as the developer. The developed plates were dipped into a 5% solution of phosphomolybdic acid in ethanol and were then placed on an electrically heated hotplate for 30 s. Components appeared as dark spots on a light greenish background. Infrared (IR) spectra were recorded on a Bio-Rad FTS-165 FT-IR spectrometer. Samples were run as neat films on NaCl windows. Nuclear magnetic resonance spectra were recorded on a Bruker Avance DPX₃₀₀ (300 MHz) Fourier-transform NMR spectrometer (Bruker, Fallanden, Switzerland) of solutions in deuterochloroform (CDCl₃, 0.2–0.3 mM) with tetramethylsilane (TMS) as the internal reference standard. Chemical shifts are given in δ-values in ppm downfield from TMS (δTMS = 0 ppm).
resolution mass spectra were recorded on a Finningan Mat 95 mass spectrometer (Finnigan Mat Corp., San Jose, CA). Santalbic acid was isolated from Santalum album seeds (purchased from Gautam Global, Dehra Dun, India. E-mail: treeseeds@operamail.com). All solvents and reagents used were of the analytical reagent grade and purchased from Aldrich Chemical Co. (Milwaukee, WI). Diethyl ether, tetrahydrofuran, n-hexane, chloroform, dichloromethane, and acetic acid were distilled before use. Methyl trans-11,12-epoxy-9-octadecynoate (1) was prepared by the epoxidation of methyl santalbate with potassium peroxomonosulfate (Lie Ken Jie and Pasha, 1998).

2.1. Preparation of methyl anti-11-fluoro-12-hydroxy-9-octadecynoate (2a)

A mixture of methyl trans-11,12-epoxy-9-octadecynoate (1) (0.5 g, 1.66 mmol) and tetrabutylammonium dihydrogen trifluoride (0.48 g, 1.6 mmol) was heated at 120 °C for 60 h. The reaction mixture was cooled, diethyl ether (100 cm³) was added and the mixture washed with water (2 cm³ × 100 cm³). The ethereal fraction was dried with Na₂SO₄ and the filtrate was evaporated. The residue was chromatographed on a silica gel (100 g) column using gradient elution with n-hexane and diethyl ether to give methyl anti-11-fluoro-12-hydroxy-9-octadecynoate (2a) (0.3 g, 57%) as a pale yellow viscous oil. TLC (silica) Rₖ = 0.63 (n-hexane/diethyl ether, 1:1, v/v, as developer); IR (neat): 3462, 2932, 2858, 2236, 1738, 1462, 1436, 1362, 1322, and 1167 cm⁻¹; ¹H NMR (CDCl₃, δp): 0.89 (t, J = 6.6 Hz, CH₃), 1.2-1.7 (m, 20H, CH₂), 2.2-2.3 (m, 2H, 8-H), 2.31 (t, J = 7.5 Hz, 2H, 2-H), 2.60 (br, OH, D₂O exchangeable), 3.67 (s, 3H, COOCH₃), 3.72-3.85 (m, 1H, 12-H) and 5.02 (ddt, J = 48.3, 3.75, 1.88 Hz, 1H, 11-H).

¹³C NMR (75.47 MHz, CDCl₃, δp): 14.00 (C-18), 18.65 (dd, J₁C,F = 3.0 Hz, C-8), 22.53 (C-17), 24.76 (C-3), 25.34 (C-14), 28.50, 28.59, 28.87, 29.12, 31.65 (C-16), 33.95 (C-2), 51.41 (COOCH₃), 72.90 (dd, J₂C,F = 22.4 Hz, C-12), 73.82 (d, J₂C,F = 26.3 Hz, C-9), 86.11 (d, J₁C,F = 169.7 Hz, C-11), 91.35 (d, J₂C,F = 10.4 Hz, C-10), and 174.22 (COOCH₃); MS: OTMS derivative: m/z (intensity, %): 380 (M-HF, 7), 308 (M-F-TMS, 57), 219 (5), 187 (base peak, 100), and 165 (62); high resolution mass spectral analysis (HRMS) found: M-HF, 380.2750, C₂₂H₄₀SiO₃ requires 380.2747.

2.2. Preparation of methyl syn-11-fluoro-12-hydroxy-9-octadecynoate (2b)

A mixture of methyl trans-11,12-epoxy-9-octadecynoate (1) (0.51 g, 1.66 mmol), boron trifluoride etherate (0.2 ml, 1.60 mmol), and chloroform (20 cm³) was stirred for 5 min at room temperature. Aqueous sodium hydrogencarbonate solution (10%, w/w, 10 cm³) was added and the reaction mixture was extracted with diethyl ether (3 cm³ × 30 cm³). The ethereal extract was washed successively with water (2 cm³ × 20 cm³), brine (30 cm³) and dried over anhydrous sodium sulfate. The filtrate was evaporated under reduced pressure and the residue was column chromatographed on silica gel (10 g) using a mixture of n-hexane and diethyl ether (98:2, v/v, 600 cm³) followed by a mixture of n-hexane and diethyl ether (4:1, v/v, 400 cm³) which eluted methyl syn-11-fluoro-12-hydroxy-9-octadecynoate (2b) (188 mg, 35%) (in addition to a mixture of methyl 12-oxo-9,10-octadecadione and methyl 12-oxo-9-octadecynoate (202 mg, 40%)). TLC (silica) Rₖ = 0.4 (n-hexane/diethyl ether, 3:2, v/v, as developer); IR (neat): 3480, 2931, 2858, 2244, 1741, 1630, 1462, 1362, 1327, 1246, 1200, 1173, 1132, 1089, 878, and 723 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, δp): 0.89 (t, J = 6.6 Hz, CH₃), 1.21-1.71 (m, 20H, CH₂), 2.19-2.33 (m, 4H, 2-H, and 8-H), 2.67 (br, OH, D₂O exchangeable), 3.67 (s, 3H, COOCH₃), 3.73 (m, 1H, 12-H), 4.89 (ddt, 1H, J = 49.6, 6.6, 1.9 Hz, 11-H); ¹³C NMR (75.47 MHz, CDCl₃, δp): 14.07 (C-18), 18.70 (J₄C,F = 3.1 Hz, C-8), 22.59 (C-17), 24.85 (C-3), 28.12, 28.15, 28.58, 28.72, 28.72, 28.95, 29.02, 29.19, 29.32, 31.65/31.71 (C-16), 34.02 (C-2), 51.46 (COOCH₃), 73.56 (d, J₂C,F = 21.9 Hz, C-12), 73.87 (d, J₃C,F = 16.6 Hz, C-9), 86.25 (d, J₁C,F = 168.8 Hz, C-11), 91.30 (d, J₂C,F = 10.5 Hz, C-10), and 174.24 (COOCH₃); MS: m/z (intensity, %): 371 (M⁺ + 1, 2), 351 (3), 350 (2), 339 (M⁺ - 31, 9), 328 (2), 309 (2), 308 (7), 297 (11), 277 (28), 256 (45), 236 (6), 224 (65), 214 (base peak, 100), 197 (28), 182 (16), 181 (9), 157 (9), 136 (31), 135 (9), and 120 (56); HRMS (acetate derivative) found: M-HF, 350.2460, C₂₁H₃₅O₄F requires 350.2457.
2.3. Preparation of methyl anti-11-chloro-12-hydroxy-9-octadecynoate (3)

A mixture of methyl trans-11,12-epoxy-9-octadecynoate (1) (0.2 g, 0.6 mmol), glacial acetic acid (0.125 g, 2 mmol), tetrahydrofuran (THF, 20 cm³) and LiCl (0.11 g, 2.5 mmol) was refluxed for 40 h. The reaction mixture was diluted with water (30 cm³) and extracted with diethyl ether (3 cm³ × 50 cm³). The ether extract was washed with water (30 cm³), dried (Na₂SO₄), and the filtrate was evaporated under reduced pressure. The residue was chromatographed using n-hexane and diethyl ether (7:3, v/v) to give methyl anti-11-chloro-12-hydroxy-9-octadecynoate (3) (0.2 g, 89%) as a viscous oil. TLC (silica) RF = 0.5 (n-hexane/diethyl ether, 1:1, v/v, as developer); IR (neat): 3472, 2932, 2856, 2225, 1740, 1460, 1437, 1246, 1200, and 1086 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, δH): 0.88 (t, J = 6.7 Hz, 3H, CH₃), 1.29–1.78 (m, 20H, CH₂), 2.22–2.29 (m, 2H, 8-H), 2.30 (t, J = 7.5 Hz, 2H, 2-H), 3.67 (s, 3H, COOCH₃), 2.67 (br, OH, D₂O exchangeable), 3.7–3.8 (m, 1H, 12-H), and 4.60 (dt, J = 3.9, 2.1 Hz, 1H, 11-H); ¹³C NMR (75.47 MHz, CDCl₃, δC): 14.08 (C-18), 18.83 (C-8), 22.60 (C-17), 24.86 (C-3), 25.61 (C-14), 28.25, 28.59, 28.67, 28.97, 29.18, 31.74 (C-16), 33.10 (C-13), 34.04 (C-2), 51.47 (COOCH₃), 55.11 (C-11), 74.72 (C-12), 75.24 (C-9), 89.70 (C-10), and 147.26 (COOCH₃); MS: OTMS derivative: m/z (intensity %): 380 (M–HCl, 5), 308 (M–Cl–TMS, 14), 188 (16), 187 (100), 165 (18), and 108 (3); HRMS (OTMS derivative) found: M–HCl, 380.2753. C₂₂H₄₀SiO₃ requires 380.2747.

2.4. General procedure for the oxidation of halohydrin as exemplified by the methyl 11-fluoro-12-hydroxy-9-octadecynoate (2a or 2b) with chromic acid

A mixture of methyl 11-fluoro-12-hydroxy-9-octadecynoate (2a or 2b) (0.2 g, 0.6 mmol) and diethyl ether (30 cm³) was stirred at 0–5°C. Chromic acid (0.5 cm³, prepared from 5 g Na₃Cr₂O₇, 7 g H₂SO₄, and 16 cm³ H₂O) was added to the reaction mixture while keeping the temperature between 0–5°C. The reaction mixture was stirred for a further 2 h. Water (50 cm³) was added and the reaction mixture was extracted with diethyl ether (3 cm³ × 50 cm³). The ethereal extract was successively washed with water (10 cm³), aqueous sodium hydrogencarbonate (10%, 50 cm³), and dried over anhydrous Na₂SO₄. The filtrate was evaporated under reduced pressure. Silica gel column chromatographic purification using n-hexane/diethyl ether (4:1, v/v) as eluent gave methyl 11-fluoro-12-oxo-9-octadecynoate (4) (0.15 g, 75%) as a viscous oil. TLC (silica) RF = 0.7 (n-hexane/diethyl ether, 1:1, v/v, as developer); IR (neat): 2932, 2859, 2212, 1746, 1694, 1436, 1436, 1363, and 1167 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, δH): 0.89 (t, J = 6.7 Hz, 3H, CH₃), 1.2–1.7 (m, 18H, CH₂), 2.2–2.32 (m, 2H, 8-H), 2.30 (t, J = 7.4 Hz, 2H, 2-H), 2.61–2.67 (m, 2H, 13-H), 3.67 (s, 3H, COOCH₃), and 5.28 (dt, J = 49.85, 2.2 Hz, 1H, 11-H); ¹³C NMR (75.47 MHz, CDCl₃, δC): 13.92 (C-18), 18.69 (d, J = 3.0 Hz, C-8), 22.93 (C-17), 24.20 (C-3)¹, 24.76 (C-14)¹, 28.49, 28.51, 28.54, 58.59, 28.64, 28.73, 28.81, 28.86, 31.42, 36.96 (d, J = 1.4 Hz, C-13), 51.35 (COOCH₃), 72.22 (d, J = 2.5 Hz, C-10), 84.48 (d, J = 1.4 Hz, C-11), 92.49 (d, J = 11 Hz, C-9), 174.05 (COOCH₃) and 202.57 (d, J = 24 Hz, C-12); MS: m/z (intensity %): 326 (M⁺, 36), 306 (M-HF, 25), 295 (M–31, 15), 197 (32), 255 (6), and 113 (100); HRMS found: M⁺, 326.2245. C₁₉H₃₁O₃F requires 326.2257.

Methyl 11-chloro-12-oxo-9-octadecynoate (5) (73% yield). TLC (silica) RF = 0.7 (n-hexane/diethyl ether, 1:1, v/v, as developer); IR (neat): 2933, 2858, 2228, 1739, 1457, 1435, 1200, and 1167 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, δH): 0.89 (t, J = 6.7 Hz, 3H, 18-H), 1.22–1.7 (m, 16H, CH₂), 2.27 (m, 2H, 8-H), 2.31 (t, J = 7.5 Hz, 2H, 2-H), 2.68–2.87 (m, 2H, 13-H), 3.67 (s, 3H, COOCH₃), and 4.85 (t, J = 2.3 Hz, 1H, 11-H); ¹³C NMR (75.47 MHz, CDCl₃, δC): 14.03 (C-18), 18.93 (C-8), 22.50 (C-17), 23.88 (C-3)¹, 24.87 (C-14)¹, 28.04, 28.63, 28.70, 28.97, 31.54 (C-16), 34.03 (C-2), 36.88 (C-13), 51.46 (COOCH₃), 52.69 (C-11), 73.41 (C-9), 91.38 (C-10), 174.22 (COOCH₃), and 199.39 (C-12); MS: m/z (intensity %): 342 (M⁺, 3), 306 (M–HCl, 1), 107 (78); HRMS found: M⁺, 342.1964. C₁₉H₃₁ClO₃ requires 342.1962.

¹ interchangeably.
2.5. General procedure for the isomerization of halo keto acetylene as exemplified by methyl 11-fluoro-12-oxo-9-octadecenoate (4)

A mixture of methyl 11-fluoro-12-oxo-9-octadecenoate (4) (0.16 g, 0.47 mmol) in dichloromethane (10 cm³) and potassium carbonate (0.1 g, 0.73 mmol) was stirred at room temperature for 30 min. The filtrate was evaporated under reduced pressure. The residue was column chromatographed on a silica column (20 g) using gradient elution with n-hexane and diethyl ether to give methyl 11-fluoro-12-oxo-9,10-octadecadienoate as a light yellow oil (6, 0.1 g, 63%). TLC (silica) Rf = 0.65 (n-hexane/diethyl ether, 1:1, v/v, as developer); IR (neat): 2931, 2858, 1954 (allene), 1739, 1692 (keto C=O), 1463, 1436, 1362, 1198, and 1172 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, δH): 0.88 (t, J = 6.8 Hz, 3H, CH₃), 1.2–1.7 (m, 18H, CH₂), 2.25–2.4 (m, 4H, 2-H, and 8-H), 2.51 (t, J = 7.5 Hz, 2H, 13-H), 3.67 (s, 3H, COOCH₃), and 6.34 (t, J = 6.8 Hz, 1H, 9-H); ¹³C NMR (75.47 MHz, CDCl₃, δC): 13.95 (C-18), 22.41 (C-17), 24.46 (C-3)¹, 24.78 (C-14)¹, 28.80, 28.88, 28.92, 29.91 (C-8), 31.47 (C-16), 33.93 (C-2), 38.13 (C-13), 51.40 (COOCH₃), 112.70 (d, ³JCF = 9.4 Hz, C-9), 135.97 (d, ¹JCF = 246.3 Hz, C-11), 174.15 (COOCH₃), 194.58 (d, ²JCF = 26.6 Hz, C-12), and 196.36 (d, ²JCF = 21.1 Hz, C-10); MS: m/z (intensity, %): 326 (M⁺, 28), 295 (M-31, 8), 241 (95), 239 (33), 197 (47), 183 (88), 154 (42), and 113 (26); HRMS found: M⁺, 326.2254, C₁₉H₃₁O₃ requires 326.2257.

Methyl 12-oxo-11-chloro-9,10-octadecadienoate (7, 80% yield). TLC (silica) Rf = 0.65 (n-hexane/diethyl ether, 1:1, v/v, as developer); IR (neat): 2930, 2858, 1942 (allene), 1738, 1698 (keto C=O), 1436, and 1370 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, δH): 0.88 (t, J = 6.7 Hz, 3H, CH₃), 1.2–1.7 (m, 18H, CH₂), 2.25–2.34 (m, 2H, 8-H), 2.31 (t, J = 7.5 Hz, 2H, 2-H), 2.58–2.65 (m, 2H, 13-H), 3.67 (s, 3H, COOCH₃), and 6.01 (t, J = 6.9 Hz, 1H, 9-H); ¹³C NMR (75.47 MHz, CDCl₃, δC): 13.94 (C-18), 22.39 (C-17), 24.77 (C-13)¹, 24.87 (C-14)¹, 28.18, 28.45 (C-8), 28.78, 28.86, 28.92, 31.46 (C-16), 33.92 (C-2), 38.71 (C-13), 51.37 (COOCH₃), 103.43 (C-9), 106.30 (C-11), 174.08 (COOCH₃), 193.75 (C-12), and 208.09 (C-10); MS: m/z (intensity, %): 342 (M⁺, 40), 311 (M-31, 7), 307 (M-Cl, 100), 275 (38), 199 (17), 185 (22), 113 (47); HRMS found: M⁺, 342.1960, C₁₉H₃₁ClO₃ requires 342.1962.

3. Results and discussion

We have earlier reported the isomerization of methyl 12-oxo-9-octadecenoate (obtained from methyl ricinoleate) to a C₁₈ oxo-allenic ester (methyl 12-oxo-9,10-octadecadienoate), which was used in subsequent reactions with various hydrazines to give pyrazole fatty ester derivatives (Lie Ken Jie and Lau, 1999). The aim of this project was to incorporate a halide function (fluoride or chloride) to the keto-allene system. The strategy was to start with methyl salts, which contains a conjugated enyne system at the 9,11-position of the alkyl chain. By epoxidizing the olefinic bond, the resulting epoxy-acetylenic derivative would readily allow the introduction of a halide ion. Regio-selective and possibly a stereoselective ring opening of the epoxy group would give a halo-hydroxy-acetylenic intermediate, which could then be oxidized to the corresponding halo-oxo-intermediate. The latter compound might then be isomerized to the requisite halo-oxo-allenic derivative.

To introduce a fluoride into the system, tetra-butylammonium dihydrogenphthalimide (Landini and Penso, 1990; Landini et al., 1988) was used to convert methyl trans-11,12-epoxy-9-octadecenoate (1) regio-and stereoselectively to methyl anti-11-fluoro-12-hydroxy-9-octadecenoate (2a) in good yield (57%) (Scheme I). The stereoselectivity of this reaction seems to be most remarkable because Camps et al. (1986) observed a totally stereo-unsensitive reaction of a comparable cis-epoxide.

The anti-fluoro-hydroxy fatty ester derivative 2a was identified by NMR spectroscopy by the appearance of a doublet of triplets for the 11-H proton, which appeared at δH 5.02 (coupling constants J₁₁-H,F = 48.3 Hz, J₁₁-H, 12-H = 3.75 Hz, and J₁₁-H, 8-H = 1.88 Hz). The methine proton attached at C-12 appeared as a multiplet at δH 3.75, while the shift of the 8-H was found at δH 2.2–2.3 (m). These shift data agreed with the proton NMR results of a similarly structured compound, anti-11-fluoro-14-hydroxyhexadec-11-ynyl acetate (Camps et al., 1986; Lan and Hammond, 2000). The presence of a fluorne atom in compound 2a was
Scheme 1. Reagents and conditions: (i) Oxone®, trifluoroacetone, NaHCO₃, CH₃CN, 1.5 h, 0-5°C; (ii) Bu₄NH₂F₂, 120°C, 60h; (iii) BF₃·Et₂O, CHCl₃, 5 min., r.t.; (iv) LiCl, THF, AcOH, reflux, 40 h; (v) chromic acid, Et₂O, 0-5°C, 2 h; (vi) K₂CO₃, CH₂Cl₂, 30 min.

further confirmed by the observation of the J constants of the critical carbon nuclei in the ¹³C NMR spectrum. The signal for the shift of the C-11 carbon atom (to which the fluorine atom is attached) resulted in a doublet (J = 169.7 Hz), due to the coupling of the carbon nucleus with the fluorine nucleus. Also, the characteristic geminal coupling (²J₁₂,F) of the C-12 carbon atom with the fluorine atom at the C-11 nucleus gave rise to a doublet at 8C 72.90 (J = 22.4 Hz). The assignment of the C-12 atom (to which the hydroxy group is attached) was confirmed by the ¹H-¹³C COSY technique. From these spectroscopic results, it was evident that the fluoride ion (from tetrabutylammonium dihydrogen trifluoride) attacked the more reactive propargylic carbon atom (C-11) of the epoxy system of methyl trans-11,12-epoxy-9-octadecenoate (I) from the anti-direction leading to the formation of the corresponding anti-halohydrin 2a (Scheme 1). This reaction was therefore predominantly regio- and stereoselective.

Ring opening of epoxide to form fluorohydrin could also be achieved using BF₃-etherate complex (Barili
et al., 1974). When methyl trans-11,12-epoxy-9-octadecynoate (1) was stirred with boron trifluoride etherate in chloroform, the corresponding syn-halo-hydride isomer 2b was isolated in 35% yield. The rest of the reaction mixture was composed of methyl 12-oxo-9,10-octadecadienoate and methyl 12-oxo-9-octadecynoate (total of 40%) (Lie Ken Jie and Lau, 1999).

The syn isomer 2b showed the characteristic chemical shift for the 11-H (on the same carbon at the fluorne atom), which appeared at δH 4.89 as a double doublet of triplets with J coupling constants (J11-H,F = 49.6 Hz, J11-H,12-H = 6.56 Hz and J11-H,8-H = 1.86 Hz). These shift data agreed with the proton NMR results of a similarly structured compound, syn-13-fluoro-14-hydroxyhexadec-11-ynyl acetate, as reported in the literature (Camps et al., 1986; Lan and Hammon, 2000). The formation of the anti-fluorohydrid fatty ester derivative 2b could be explained by the following plausible mechanism: the strong Lewis acid (boron trifluoride) reacts with the epoxy system of substrate 1 to yield a BF3-complex; ring opening of the epoxy system gives a carboxylation intermediate where the electron deficient carboxylation is subsequently attacked by one of the fluorne atoms of the BF3-complex in a syn-manner to give the requisite anti-isomer.

Reaction of compound 1 with lithium chloride in THF/glacial acetic acid gave the corresponding chlorohydrid derivative 3. Similar to the reactions with fluorde (from tetraethylammonium dihydrogentrifluoride), the chloride ion approached substrate 1 from the anti-direction and attacked the epoxy carbon atom adjacent to the triple bond (the propargylic position). This reaction gave exclusively methyl anti-11-chloro-12-hydroxy-9-octadecynoate (3) in 89% yield. The structure of the chloro-hydroxy acetylenic intermediate 3 was identified from the NMR spectroscopic and mass spectrometric results. Final confirmation of the structure of compound 3 was achieved by homonuclear multiple bonds correlation (HMBC) technique as described below:

![Homonuclear Multiple Bonds Correlation (HMBC) of compound 3.](image)

Two-phase chomic acid oxidation (Lie Ken Jie and Kalluri, 1997) was carried out on the fluoro- and chloro-hydroxy-acetylenic intermediates 2a, 2b, and 3 to furnish the corresponding fluoro-oxo (4) and chloro-oxo-acetylenic (5) C18 fatty ester derivatives with an average yield of 72%. The 1H NMR spectral analysis of compounds 4 and 5 agreed well with the anticipated shift values for all protons, except for the 13-H protons. These protons appeared as a multiplet instead of a triplet. A possible explanation for the appearance of a multiplet for the shift of the 13-H proton could be made from the fact that compounds 4 and 5 have a stereocenter at C-11. As a result, the two protons at C-13 position experience different magnetic environments, which caused them to couple with one another and in turn with the protons of their adjacent methylene protons (14-H) to give a multiplet.

![Structure of compound 3.](image)

When methyl 11-fluoro-12-oxo-9-octadecynoate (4) and methyl 11-chloro-12-oxo-9-octadecynoate (5) were treated with potassium carbonate in dichloromethane at room temperature, methyl 11-fluoro-12-oxo-9,10-octadecadienoate (6, 63%) and methyl 11-chloro-12-oxo-9,10-octadecadienoate (7, 80%) were obtained, respectively. The IR spectra showed the stretching vibrations of the allene system at 1954 and 1942 cm⁻¹ for compound 6 and 7, respectively. The unique effect of the fluorne nucleus was again clearly reflected in the NMR spectral analyses.

The coupling of the fluorne nucleus with C-9, C-10, C-11, and C-12 gave characteristic doublets with J constants of 9.4 Hz (for C-9, 21.1 Hz (for C-10), 26.6 Hz (for C-12), and 246.3 Hz with C-11 (to which the fluorne atom is attached). These unique spectroscopic features of the fluoro-allene fatty ester 6 are the first to be reported for such a lipid derivative. In compound 7, the incorporation of the chlorine atom to the allene system caused the allenic carbon nuclei to appear at δC 103.43 (C-9), 208.09 (C-10), and 106.30 (C-11) while the shift of the keto carbon atom (C-12) appeared at δC 193.75 (C-12). These results agreed with those reported by Crandall et al. (1992).
Santalbic acid (from *Santalum album*) is therefore an excellent starting material for the preparation of a wide range of novel and exotic fatty acid derivatives. The enyne system in the alkyl chain of this substrate allowed specific reactions, such as the epoxidation of the olefinic bond, to be carried out. The resulting epoxy-acycylene derivative becomes a very reactive intermediate, which allows the incorporation of various nucleophiles (such as halides) through regions as well as stereoselective ring opening of the epoxy system. Oxidation of the haloxydrins furnishes key keto-acycyclic intermediates, which are readily isomerized to yield novel fluoro- and chloro-oxo-allenic fatty ester derivatives.

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