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Stereoselective Synthesis of Methyl (11S,12S,13S)-(9Z,15Z)-11-Hydroxy-12,13-Epoxy Octadecadienoate from D-Mannose

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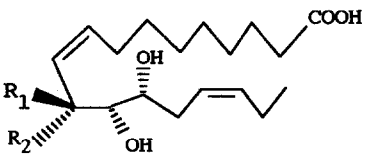
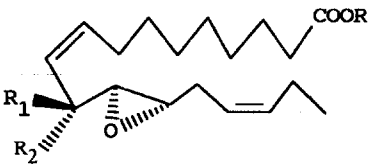
Abstract: The title compound, a self defensive substance against the rice blast disease, was synthesized from D-mannose in ten steps. The key intermediate **6** was prepared with Grignard addition of lactol **5** in favoured anti selectivity.

In recent years, several oxygenated C_{18}-fatty acids, such as compounds **1-4**, have been isolated from rice plants suffering from rice blast disease, and proved to be self defensive substances against the disease[1]. Because the rice blast disease is a severe problem for the production of rice in China and other countries, syntheses of such relatively rare compounds and use of them for the investigation of the disease promise to be especially interesting. However, up to now only a few reports have been published[2-5], among which only two papers, an asymmetric synthesis based on the Sharpless kinetic resolution[2] and a nonselective rearrangement of allylic hydroperoxide[4], were about the synthesis of title compound. As part of continuous effort to the synthesis of lipoxygenase metabolite of fatty acid using carbohydrate and hydroxy acids as the chiral pool, we have succeeded in syntheses of compound **1** and **3** from L- and D-tartaric acid respectively. Herein we would like to describe the synthesis of another member in this family, compound **4a**, from D-mannose.



1 R_1 = OH, R_2 = H

2 R_1 = H, R_2 = OH



3 R_1 = H, R_2 = OH, R = H

3[a] R_1 = H, R_2 = H, R = Me

4 R_1 = OH, R_2 = H, R = H

4[a] R_1 = OH, R_2 = H, R = Me

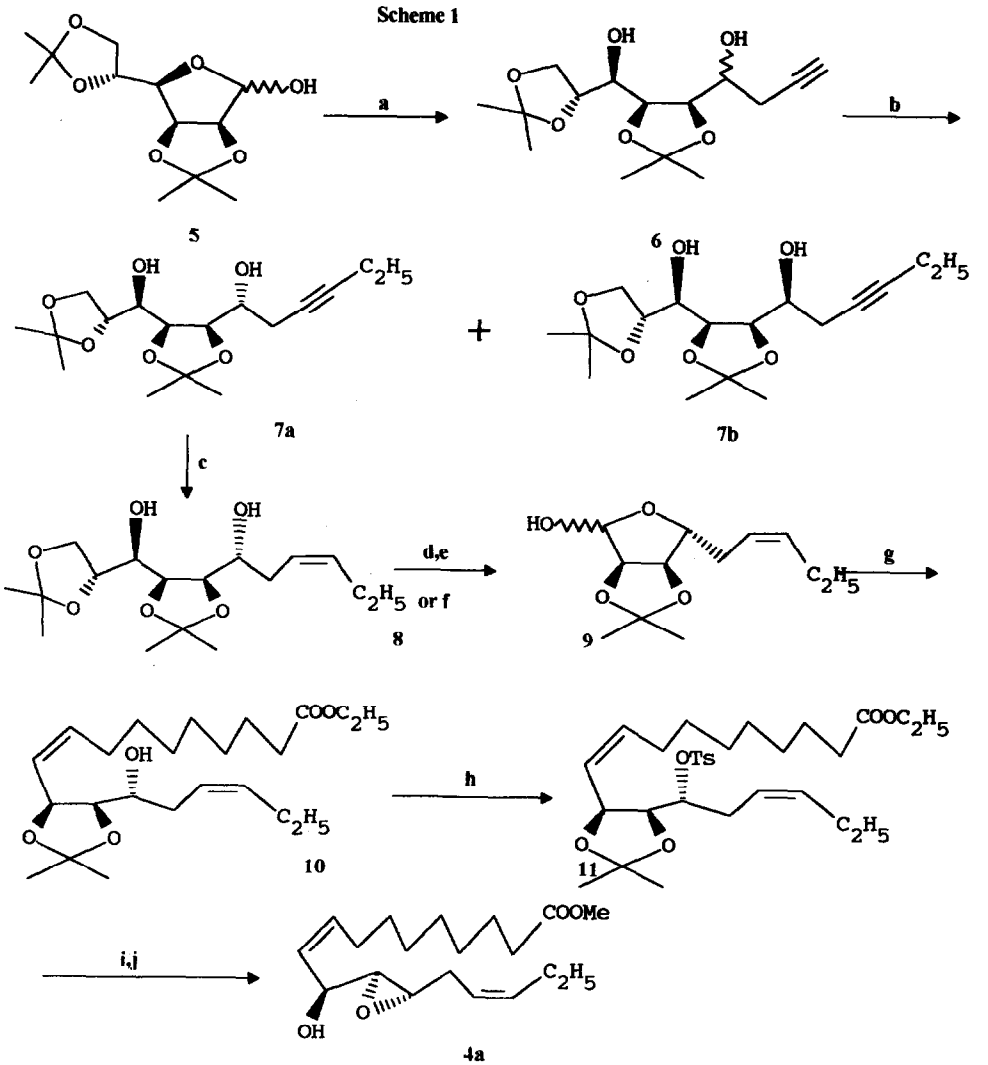
Comparing the stereochemistry of compound **4** with D-mannose showed that the relationship of 3R and 4R-erythro-configuration of the latter was exactly the same as that of C_{12} and C_{11} in compound **4**. Hence, we were planning to utilize the 3R,4R-chiral center for the first two (C_{12} and C_{11}) chiral centers of title compound and also as a template to build the third one by a stereoselective reaction. There are several cases in the literature where the reaction of 2,3-O-isopropylidene derivatives of furanose sugar yielded the product with satisfied erythro (i.e., anti) selectivity[6]. Thus 2,3:5,6-di-O-isopropylidene-D-manno-furanose (**5**) prepared from D-mannose by known procedure[7] was reacted with propargyl Grignard reagent[8] in ether to afford quantitatively a diastereomeric mixture **6**, which was inseparable by usual column chromatography. Treatment of the terminal alkyne **6** with ^{n}butyllithium and ethyl bromide in THF-HMPA followed by chromatography yielded the erythro-isomer **7a** (70%) and the threo-isomer **7b** (12%). Partial hydrogenation of pure **7a** over Lindlar catalyst produced (Z)-alkene **8** in 97% yield.

Chemoselective cleavage of the 1,2-O-isopropylidene of **8** with 70% AcOH followed by $NaIO_4$ cleavage of the resulting glycol furnished the lactol **9** in 50 % yield in two steps. Recently we[9] found that this conversion could be realized by simple treatment of **8** with periodic acid in dry ether in 92% yield.

The remaining nine-carbon chain of the target molecule were then introduced by a Wittig reaction. Reaction of lactol **9** with ethyl 9-(triphenylphosphorylidene)-nonanoate under cis-olefination conditions led to the (Z,Z)-product **10** in 38 % yield.

Tosylation of **10**, deketalization of **11** accompanied with the ester exchange during treatment with PTS in MeOH, and treatment with K_2CO_3 afforded the title compound **4a**, $[\alpha]_D^{20}$ +72.4°(c 0.89, acetone), its ^{1}HNMR data prepared here was in accord with the data recorded in the literature[1b].

Scheme 1



a) $CH{=}CHCH_2MgBr$; b) n-BuLi-THF; HMPA-BrC_2H_5; c) H_2, Pd-Pb-$CaCO_3$; d) 70% AcOH; e) $NaIO_4$, H_2O; f) H_5IO_6, dry ether; g) $Br^-Ph_3P^+C_8H_{16}COOEt$, $KN(SiMe_3)_2$, THF; h) *p*-TsCl, Py; i) PTS, MeOH; j) K_2CO_3, MeOH

Experimental Section.

General procedures. Melting points are uncorrected. IR spectra were run on a Schimadzu 440 spectrometer. ^1H NMR spectra were recorded with TMS as an internal standard at 200 MHz or 300 MHz spectrometer. MS spectra (EI) were obtained on a Finnigan 4201 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 Autopol polarimeter. Flash column chromatography was performed on silica gel H(10-40m), and with petroleum ether/ethyl acetate system as eluent. The phrase " dried and evaporated " indicates drying with Na_2SO_4, followed by evaporation of the solvents under house vacuum.

Terminal alkyne 6. A small quantity of propargyl bromide was added to magnesium (4.0 g, 0.167 mol) and mercuric chloride (0.3 g)in ether (50 mL). Once the reaction had been initiated by gentle heating, the solution was cooled to 0°C and the remainder of the propargyl bromide (22.0 g, 0.185 mol)in ether (150 mL) was slowly added. The solution was cooled to -70°C, then the starting material **5** (13.0 g, 50 mmol) was added portionwise, the reaction mixture was stirred at -70°C for 2 h and -70°C to 0°C for additional 2 h, then poured into a saturated solution of NH_4Cl. Usual work-up and chromatography gave **6**(15 g, 100 %) as a mixture of diastereoisomer. IR(film) 3450(OH), 3290(≡ -H), 2100(C≡C) cm^{-1}; ^{1}HNMR(200 MHz, $CDCl_3$) 1.36(s, 3H), 1.38(s, 3H), 1.42(s, 3H), 1.47(s,3H), 2.09(t, J = 2.2 Hz, 1H), 2.4-2.60(m, 2H), 3.9-4.20(m, 6H), 4.43(m, 1H); MS(m/z) 301(M^++1, 40 %), 285(M^+-Me, 30), 283(M^++1-H_2O,3); HRMS calcd for $C_{14}H_{21}O_6$ (M^+-Me) 285.1338; obsd 285.1305.

1,2:4,5-Di-O-isopropylidene-8-undecyne-D-glycero-D-manno-1,2,3,4, 5,6-hexol (7a) and (6S)-isomer 7b. To a stirred solution of **6** (9.0 g, 30 mmol) in dry THF (160 mL) was added n-BuLi (97.5 mmol) dropwise at -30°C. After 30 min, a solution of BrC_2H_5 (5.0g, 46 mmol) in HMPA (25 mL) was added. Stirring was continued for 1 h at -50°C and -50°C to 10°C overnight. The reaction was quenched with saturated solution of NH_4Cl, the aqueous layer was extracted with ether. The organic layers were combined, washed with brine, dried and evaporated. The residue was chromatographed to give the anti-isomer **7a** (6.89 g, 70 %), $[\alpha]_D^{20}$ -10.7° (c 0.5, $CHCl_3$); IR(film) 3450(OH), 2100(C≡C) cm^{-1}; ^{1}H NMR(200 MHz, CD_3COCD_3) 0.80(t, J = 7.5 Hz, 3H), 1.16(s, 3H), 1.21(s, 6H), 1.31(s, 3H), 1.47(s, 3H), 2.10(m, 2H), 2.2-2.50(br, OH), 2.62(m, 2H), 3.7-4.10(m, 7H); MS(m/z) 329(M^++1), 313(M^+-Me), 311(M^++1-H_2O). HRMS calcd for $C_{16}H_{25}O_6$(M^+-Me) : 313.1651; Obsd 313.1610. Syn-isomer **7b** (1.18 g, 12 %), m.p. 77-78°C; $[\alpha]_D^{20}$ +2.5° (c 1.2, $CHCl_3$); IR(KBr) 3450(OH), 2100(C≡C) cm^{-1}; ^{1}H NMR(200MHz, CD_3COCD_3) 1.09(t, J =7.5 Hz, 3H), 1.31(s, 3H), 1.34(s, 3H), 1.36(s, 3H), 1.47(s, 3H), 2.15(m, 2H), 2.48(m, 2H), 3.70(m, 1H), 3.9-4.20 (m, 4H), 4.40(m, 2H); MS(m/z) 329(M^++1, 1 %), 313, 311; HRMS calcd for $C_{16}H_{25}O_6$(M^+-Me) 313.1651; Obsd 313.1659.

1,2:4,5-Di-O-isopropylidene-8(Z)-undecene-D-glycero-D-manno-1,2, 3,4,5,6- hexol (8). The alkyne **7a** (8.4 g, 25.6 mmol) was hydrogenated under atmospheric pressure using Lindlar catalyst (1.0 g) in ethyl acetate (150 mL) in the presence of quinoline (0.5 g). After uptake of the theoretical amount of hydrogen, the mixture was filtered, and the filtrate was washed with 2N HCl and aqueous $NaHCO_3$, dried and evaporated. Chromatography of the residue produced corresponding alkene compound **8** (8.21 g, 97 %), $[\alpha]_D^{20}$ -23.9° (c 0.4, $CHCl_3$); IR(film) 3450 cm^{-1}; ^{1}H NMR(200 MHz, $CDCl_3$) 0.98(t, J = 7.5 Hz, 3H), 1.36(m, 3H), 1.39(s, 3H), 1.41(s, 3H), 1.49(s, 3H), 2.0-2.6(m, 4H), 3.90-4.41(m, 7H), 5.42(m, 1H), 5.61(m, 1H); MS(m/z) 331(M^++1), 315(M^+-Me),

313(M^++1-H_2O). Anal. Calcd for $C_{17}H_{30}O_6$: C, 61.80; H, 9.15. Found : C, 61.95; H, 9.36.

2,3-O-Isopropylidene-6(Z)-nonene-L-ribofuranose (9). Procedure A. Alkene **8** (3.0 g, 9.15 mmol) was dissolved in 70 % AcOH (50 mL), the mixture was stirred for 2 h at 40°C. After removal of the solvent under reduced pressure, the residue was dissolved in MeOH (20 mL), and added to a solution of $NaIO_4$ (4.3 g, 20 mmol) in H_2O (80 mL). The mixture was stirred for 4 h at room temperature and extracted with ether. The combined organic layers were washed with brine, dried and evaporated. Chromatography of the residue afforded lactol **9** (1.04 g, 50 %), $[\alpha]_D^{20}$ -3.9° (c 0.75, $CHCl_3$); IR(film) 3450(OH), 1660(C=C), 1380, 1370 cm^{-1}; ^1H NMR(200 MHz,$CDCl_3$) 0.96(t, J = 7.5 Hz, 3H), [1.32(s), 1.48(s), α; 1.38(s), 1.56(s), β;α/β 3:2, 6H], 2.0-2.50(m, 4H), 4.18(m, 1H), 4.4-4.70 (m, 2H), 5.3-5.60(m, 3H); MS(m/z) 229(M^++1), 213(M^+-Me), 211(M^++1-H_2O). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found : C, 63.03; H, 8.92.

Procedure B. To a solution of H_5IO_6 (0.34 g, 1.5 mmol) in dry ether (20 mL) was added alkene **8** (0.165 g, 0.5 mmol), the mixture was stirred at room temperature for 4 h. The organic layer was decanted and washed with aqueous $NaHCO_3$, brine, dried and evaporated. Chromatography gave lactol **9** (0.105 g, 92 %), the spectroscopic data are full in accord with that of the sample prepared by procedure A.

Ethyl 11(S),12(R)-O-isopropylidene-11,12,13(R)-trihydroxy-octadeca-9,15(Z)-dienoate (10). To a suspension of (8-ethoxycarbonyl-octanyl) triphenyl phosphonium bromide (3.0 g, 6 mmol) in dry THF (50 mL) was added dropwise potassium bis(trimethylsilyl)amide [$KN(SiMe_3)_2$] (1M, 6.0 mmol) at 0°C. The red solution was obtained after stirring for an additional 1 h at 0°C. The solution was cooled to -70°C, and a solution of lactol **9** (0.40 g, 1.74 mmol) was added dropwise. The reaction mixture was brought to room temperature overnight. It was extracted with ether/petroleum ether (1 :1) after addition of saturated solution of NH_4Cl. The combined extracts were washed with brine, dried and evaporated. The oily residue was chromatographed to give **10** (0.26 g, 38 %), $[\alpha]_D^{20}$ +17.4°(c 0.6, $CHCl_3$); IR(film) 3450(OH), 1735(COOMe), 1660(C=C), 1380, 1370 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) 0.90(t, J = 7.5 Hz, 3H), 1.28(t, J = 7.2 Hz, 3H), 1.3-1.70(m, 10H), 1.46(s, 3H), 1.49(s, 3H), 1.9-2.5(m, 8H), 3.70(m, 1H), 4.02(dd, J = 6.2, 8.5 Hz, 1H), 4.15(q, J = 7.2 Hz, 2H), 5.03(dd, J = 8.5, 5.8 Hz, 1H) , 5.25-5.50(m, 3H), 5.65(m, 1H); MS(m/z)381(M^+-Me), 379 (M^++1-H_2O).

Methyl 11(S)-hydroxy-12,13(S,S)-epoxyoctade-9,15(Z)-dienoate (4a). To a solution of **10** (0.2 g, 0.5 mmol) in dry CH_2Cl_2 (2 mL) was added p-TSCl (0.2 g) and pyridine (0.2 mL). The mixture was stirred at room temperature overnight, usual work-up furnished crude tosylate **11**. To a solution of thus obtained **11** in MeOH (5 mL) was added PTS (0.1 g). After stirring for 24 h at room temperature, K_2CO_3 (0.5 g) was added, the reaction mixture was stirred for additional 30 min, diluted with ethyl acetate. The organic layer was evaporated in vacuo and chromatographed to give the known methyl dienoate **4a** [1b](64 mg, 61 % from **10**) and the recovered starting tosylate **11** (methyl ester, 48 mg). **4a**, $[\alpha]_D^{20}$ +72.2° (c 0.89, $CHCl_3$); IR(film) 3450(OH), 1735(COOMe), 1660(C=C) cm^{-1}; ^1H NMR(600 MHz, $CDCl_3$) 0.97(t, J = 7.5 Hz, 3H), 1.3-1.70(m, 10H), 2.0-2.18(m, 4H), 2.30(t, J = 7.5 Hz, 2H), 2.41(m, 2H), 2.84(dd, J = 2.7, 2.3 Hz, 1H), 3.05(dt, J = 5.4, 2.3 Hz, 1H), 3.67(s, 3H), 4.66(dd, J = 8.8, 2.7 Hz, 1H), 5.32(dd, J = 11.0, 8.8 Hz, 1H), 5.34(dt, J = 10.8, 7.3 Hz, 1H), 5.54(dt, J = 10.8, 7.3 Hz, 1H), 5.64(dt, J = 11.0, 7.4 Hz, 1H); MS(m/z)325(M^++1-H_2O, 100 %), 289, 275, 227, 213.

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