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SYNTHESIS OF 13-HYDROXY-9Z,11E,15Z-OCTADECATRIENOIC ACID

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ABSTRACT : Stereoselective synthesis of 15,16-didehydro coriolic acid, starting from pent-2-en-4-yn-1-ol is described.

Synthesis of polyunsaturated hydroxy fatty acids is an interesting area of research[1] since they play an important role in biological systems along with their complex structural features. 15,16-Didehydro coriolic acid (**1**)[2], belonging to the family of oxyoctadecenoids, was isolated[3] from the resistant cultivar of rice plant Fukuyaki (Oryza sativa L) and demonstrated to act as self defensive substance; which was earlier reported[4,5] to be as anti conidial germination substance. Herein, we describe the total synthesis of **1** by a convenient approach to make the compound available in larger quantities for biological screening.

Based on the retrosynthetic analysis our general strategy is depicted in scheme 1. Accordingly, **1** could be conveniently made from **2** by a sequential Grignard followed by a Wittig reaction. **2** in turn could be successfully obtained from **4**, which facilitates both the requisite C-C bond formation as well as stereoselective incorporation of cis-double bond.

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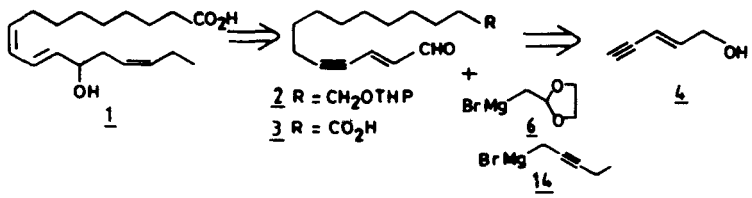
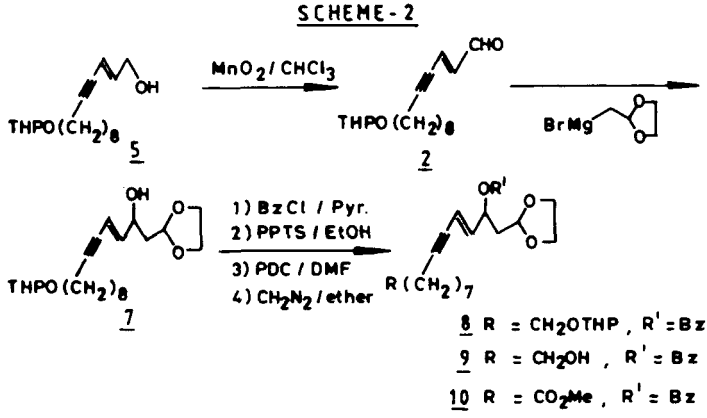
SCHEME-1



Accordingly, the known[6] alcohol **4** (scheme 2) on alkylation with 1-tetrahydropyranyloxy-8-bromo octane in presence of $LiNH_2$/liq. NH_3 gave **5** in 70% yield, which on oxidation with active MnO_2 in chloroform afforded **2** in 89% yield.

SCHEME-2



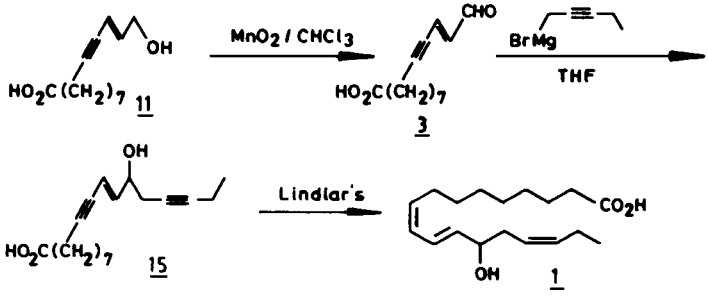
Having made the requisite aldehyde **2** in two steps, next it was aimed at the introduction of the β-hydroxy aldehyde unit by a two carbon Grignard reagent of 2-bromomethyl 1,3-dioxalane. Thus treatment of **2** with Grignard reagent **6** gave the carbinol **7** in 75% yield, where the aldehyde functionality is in the masked form. Benzoylation of **7** (85%) followed by depyranylation of **8** with PPTS in ethanol gave the alcohol **9** in 80% yield. Compound **9** on oxidation with PDC in DMF followed by treatment with ethereal diazomethane afforded the ester **10**.

Finally it was planned to unmask the aldehyde functionality in **10** which will enable the extension of three carbon unit. Attempts for the deprotection of the ketal moiety in **10**, under a variety of acid catalysed reaction conditions however met with failure.

Due to the unsuccessful unmasking of the ketal moiety in **10**, the strategy was relooked and planned to incorporate the requisite four carbon unit by making use of (Z) 1-bromo-but-2-yne (**12**).

Accordingly alkylation of **4** (scheme 3) with 8-bromo octanoic acid in presence of $LiNH_2$ in liq. NH_3, followed by oxidation of **11** by MnO_2 in $CHCl_3$ gave the aldehyde **3** in 60% yield.

SCHEME-3



The four carbon unit **12** was made in two steps from propargyl alcohol. Thus, alkylation of propargyl alcohol with ethyl bromide, followed by the reaction of pent-2-yn-1-ol (**13**) with PBr_3 in ether gave **12** in 84% yield.

Treatment of **3** with the Grignard reagent **14** made from **12** gave the carbinol **15** in 58% yield. Finally semi hydrogenation of **15** over Lindlar catalyst afforded **1** in 94% yield, whose spectral data was in agreement with the reported data.

EXPERIMENTAL

(E)-13[(Tetrahydro-2H-pyran-2-yl)-oxy]tridec-2-en-4-yn-1-al (2):

To a solution of **5** (11.76 g, 40 mmol) in chloroform (350 ml), MnO_2 (100 g) was added and stirred at room temperature for 5 h. The reaction mixture was filtered and concentrated to give the aldehyde **2** (10.39 g) in 89% yield as an oil. ^1H NMR ($CDCl_3$): δ 1.26-1.83 (m, 18H), 2.46 (dist. t, 2H), 3.20-3.96 (m, 4H), 4.56 (brs, 1H), 6.23-6.53 (m, 2H, olefinic), 9.50 (dd, 1H, -CHO): IR (Neat): 1710, 2220 cm^{-1}. Mass: M^+ 292.

Anal. Calcd. for $C_{18}H_{30}O_3$: C, 73.97; H, 9.60. Found: C, 73.89; H, 9.60%.

(E)-13-Hydroxy-tridec-11-en-9-yn-oic acid (3):

Oxidation of **11** (4.48 g, 20 mmol) in chloroform (150 ml), with MnO_2 (40 g) under the above conditions gave the aldehyde **3** (2.68 g) in 60% yield as a solid m.p. 51-52°. ^1H NMR ($CDCl_3$): δ 1.1-1.8 (m, 10H), 2.1-2.4 (m, 4H), 6.0-6.6 (m, 2H, olefinic), 9.8 (dd, 1H, -CHO), 10.0 (brs, 1H, -COOH). IR (Nujol): 1690, 3200, 2100 cm^{-1}.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.27; H, 8.10. Found: C, 70.52; H, 8.08%.

(E)-1[(Tetrahydro-2H-pyran-2-yl)-oxy]-13-hydroxy-15,15-ethylene-dioxy-pentadec-11-ene-9-yn (7):

A solution of aldehyde **2** (10 g, 34 mmol) in THF (20 ml) was treated with freshly prepared Grignard reagent (prepared from 2-bromomethyl-1,3-dioxalane (8.43 g, 50 mmol) and magnesium (1.22 g, 51 mmol) in THF (30 ml) and allowed to stir for 24 h. It was quenched with ammonium chloride solution and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), evaporated and the residue was purified by column chromatography (si-gel, pet-ether:ethyl acetate 4:1) to afford **7** (9.75 g) in 75% yield. ^1H NMR ($CDCl_3$): δ 1.20-1.75 (m, 18H), 1.75-2.0 (m, 2H), 2.25 (m, 2H), 3.2-4.2 (m, 9H), 43.55 (brs, 1H), 5.0 (m, 1H), 5.4-6.2 (m, 2H, olefinic); IR (Neat): 2210, 3450 cm^{-1}.

E-13-Benzoyloxy-1[(tetrahydro-2H-pyran-2-yl)0xy]-15,15-ethylene-dioxy-pentadec-11-ene-9-yn (8):

To a stirred solution of the alcohol **8** (9.69 g, 25.5 mmol) in dry pyridine (50 ml) at 0°C, benzoyl chloride (4.9 g, 35 mmol) was added dropwise. After 6 h at room temperature, it was quenched with ice-cold water and the aqueous layer was extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to furnish the benzoate **8** (10.49 g) in 85% yield as a viscous oil. ^1H NMR ($CDCl_3$): δ 1.15-1.70 (m, 18H), 1.9-2.3 (m, 4H), 3.1-3.9 (m, 8H), 4.5 (brs, 1H), 4.95 (m, 1H), 5.4-6.2 (m, 3H), 7.25-7.50 (m, 3H, Ar-H), 7.90-8.10 (m, 2H, Ar-H); IR (Neat): 1720 cm^{-1}.

(E)-13-Benzoyloxy-15,15-ethyledenedioxy-pentadec-11-en-9-yn-1-ol (9):

A solution of benzoate **8** (4.84 g) in ethanol (60 ml) containing PPTS (0.1 g) was stirred at 55°C. for 2 h. Ethanol was removed, the

residue was treated with ether and the ethereal layer was evaporated. The residue obtained was purified by column chromatography (Si gel, pet-ether:ethyl acetate 4:1) to afford **9** (3.2 g) in 80% yield as an oil. ^{1}H NMR ($CDCl_3$): δ 1.15-1.70 (m, 12H), 1.9-2.4 (m, 5H), 3.65 (t, 2H), 3.9 (m, 4H), 4.98 (m, 1H), 5.50-6.25 (m, 3H), 7.25-7.60 (m, 3H), 7.95-8.15 (m, 2H, Ar-H). IR (Neat): 1720, 3350 cm^{-1}.

Methyl (E)-13-benzoyloxy-15,15-ethylenedioxy pentadec-9-yn-11-enoate (10):

To a stirred suspension of pyridinium dichromate (6 g, 16 mmol) in DMF (25 ml) was added a solution of the alcohol **9** (3.2 g, 8 mmol) in DMF (5 ml) at room temperature. After 16 h, it was diluted with water and extracted with ether. The ethereal extracts were washed with water, dried (Na_2SO_4) and evaporated to give the acid.

Ethereal solution of the above acid at 0°C was treated with ethereal diazomethane. Evaporation of solvent and chromatographic purification of the resulting residue (Si-gel, pet-ether:ethyl acetate 4:1) furnished the ester **10** (1.71 g) in 50% yoverall yield. ^{1}H NMR ($CDCl_3$): δ 1.2-1.8 (m, 10H), 1.95-2.40 (m, 6H), 3.7 (s, 3H), 3.8-3.95 (m, 4H), 5.0 (m, 1H), 5.5-6.22 (m, 3H), 7.25-7.55 (m, 3H), 7.9-8.1 (m, 2H, Ar-H).

1-Bromo-pent-2-yne (12):

A mixture of alcohol **13** (3 g, 35.7 mmol) and pyridine (catalytic) in anhydrous ether (50 ml) at 0°C was treated with PBr_3 (3.22 g, 11.9 mmol). The reaction mixture was stirred for 3 h at room temperature, quenched with saturated aqueous NaBr solution. Organic layer was separated, washed with water, dried (Na_2SO_4), concentrated and filtered through silica gel with hexane to provide bromide **12** (4.4 g) in 84 yield. ^{1}H NMR ($CDCl_3$): δ 1.1 (t, 3H), 2.14-2.67 (dist. q, 2H), 4.0 (dist.t, 2H).

(E)-13-Hydroxy octadec-9,15-diyn-11-enoic acid (15):

A solution of **12** (1.83 g, 12.5 mmol) in ether (10 ml) was added to magnesium (0.3 g, 12.5 mmol) in ether (6 ml) over a period of 20 min. at room temperature under N_2 atmosphere while stirring. After 1 h, a solution of aldehyde **3** (1.11 g, t mmol) in THF (25 ml) was added dropwise and allowed to stir overnight. The mixture was

quenched with aqueous ammonium chloride and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give **15** (1.10 g) in 58% yield as an oil. ^1H NMR ($CDCl_3$): δ0.9 (dist. t, 3H), 1.1-1.8 (m, 10H), 2.4 (m, 8H), 4.1 (m, 1H), 5.6-5.8 (d, 1H, olefinic), 5.9-6.1 (dd, 1H, olefinic), 5.9 (broad s, 2H, -COOH and -OH). IR (Neat): 3300, 2200, 1700 cm^{-1}. Mass: M^+ 294.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 73.48; H, 10.20. Found: C, 73.20; H, 10.22%.

13-Hydroxy-9Z,15Z,11E-octadecatrienoic acid (1):

A mixture of the hydroxy acid **15** (0.44 g) and Lindlar's catalyst (0.15 g) in ethanol (8 ml) containing two drops of quinoline was subjected to hydrogenation at atmospheric pressure. After the absorption of required amount of hydrogen the suspension was filtered and washed with ethanol. Ethanol was evaporated, the residue obtained was dissolved in ether, washed with dil. HCl, water, dried (Na_2SO_4) and evaporated to give **1** (0.42 g) in 94% yield as an oil. ^1H NMR ($CDCl_3$): δ 0.9 (dist. t, 3H), 1.2-1.8 (m, 10H), 2.1-2.4 (m, 8H), 4.1 (m, 1H, -CH-OH), 5.5-6.3 (m, 8H, 6 olefinic, -OH and -COOH). IR (Neat): 3350, 1700 cm^{-1}. Mass : M^+ 296.

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