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A STEREOSELECTIVE SYNTHESIS OF CORIOLIC ACID AND DIMORPHECOLIC ACID

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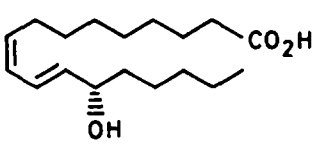
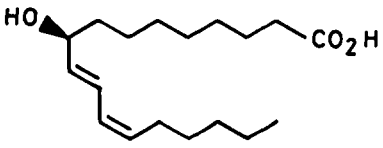
Abstract A convenient stereoselective synthesis of coriolic acid (1) and dimorphecolic acid (2), the two natural divalent cation ionophores and the self defensive substances in rice plant against rice blast disease, is described.

Unsaturated hydroxy fatty acids play important role in biological systems. Coriolic acid (1)[1] and dimorphecolic acid (2)[2] belonging to the family of oxyoctadecadienoate congeners were isolated from bovine heart mitochondria and shown to possess cation-specific ionophoric activity[3]. Both these compounds have been isolated from the resistant cultivar of rice plant Fukuyuki (Oryza sative L.) and demonstrated to act as self defensive substances against rice blast disease[4]. In addition, compounds 1 and 2 are also present in sera of patients with familial Mediterranean fever[5] (FMF) and may have a role in the pathogenesis of FMF. These findings attracted considerable attention[6,7] towards their total synthesis and as an aid to the further pharmacological evaluation herein we present the details of our efforts[8] towards the synthesis of 1 and 2.



(1)



(2)

The strategy for the construction of 1 is depicted in Scheme 1 which involves the preparation of terminal acetylenic alcohol via acetylene-zipper reaction followed by Cadiot-Chodkiewicz type coupling reaction to yield 1,3-diyne system and further aliphatic chain elaboration by Grignard reaction.

Thus tetrahydrofurfuryl chloride on reaction with n-pentyl bromide in presence of lithium amide in liquid ammonia[9] gave the 4-decyn-1-ol (3) which was converted to the terminal acetylenic alcohol 4 via acetylene-zipper reaction[10] using sodamide in 1,3-diaminopropane in 73% overall yield. 9-Decyn-1-ol (4) was protected as its THP ether 5 which was then treated with 3-bromo-2-propyn-1-ol (6)[11] in presence of cuprous chloride and hydroxylamine hydrochloride in methanol[12] to give the diacetylenic alcohol 7 in 80% yield. 7 on selective LAH reduction[13] afforded the allylic alcohol 8, a key intermediate in the synthesis of 1, in almost quantitative yield. Compound 8 not only possesses strategically situated functionalities for the eventual elaboration of aliphatic chain but also allows the introduction of carboxyl group during the penultimate stage of the synthetic sequence. In addition the acetylenic bond will serve as a precursor for the cis double bond at the final step to complete the synthesis of 1. The alcohol on oxidation with activated manganese dioxide in chloroform gave the aldehyde 9 in 89% yield. 9 on Grignard reaction with n-pentyl magnesium bromide in ether afforded the alcohol 10 in 69% yield, which was protected by benzoylation to give 11 in 85% yield. Depyranylation of 11 using pyridinium p-toluene sulphonate (PPTS)[14] yielded benzoate-alcohol 12 in 78% yield. Direct oxidation of 12 as well as its THP ether 11 with Jones reagent led to a complex mixture. However, step-wise oxidation of alcohol 12 with pyridinium dichromate in CH_2Cl_2 resulted in the formation of corresponding aldehyde 13 which was directly subjected to alkaline silver oxide oxidation followed by esterification with etherial diazo-

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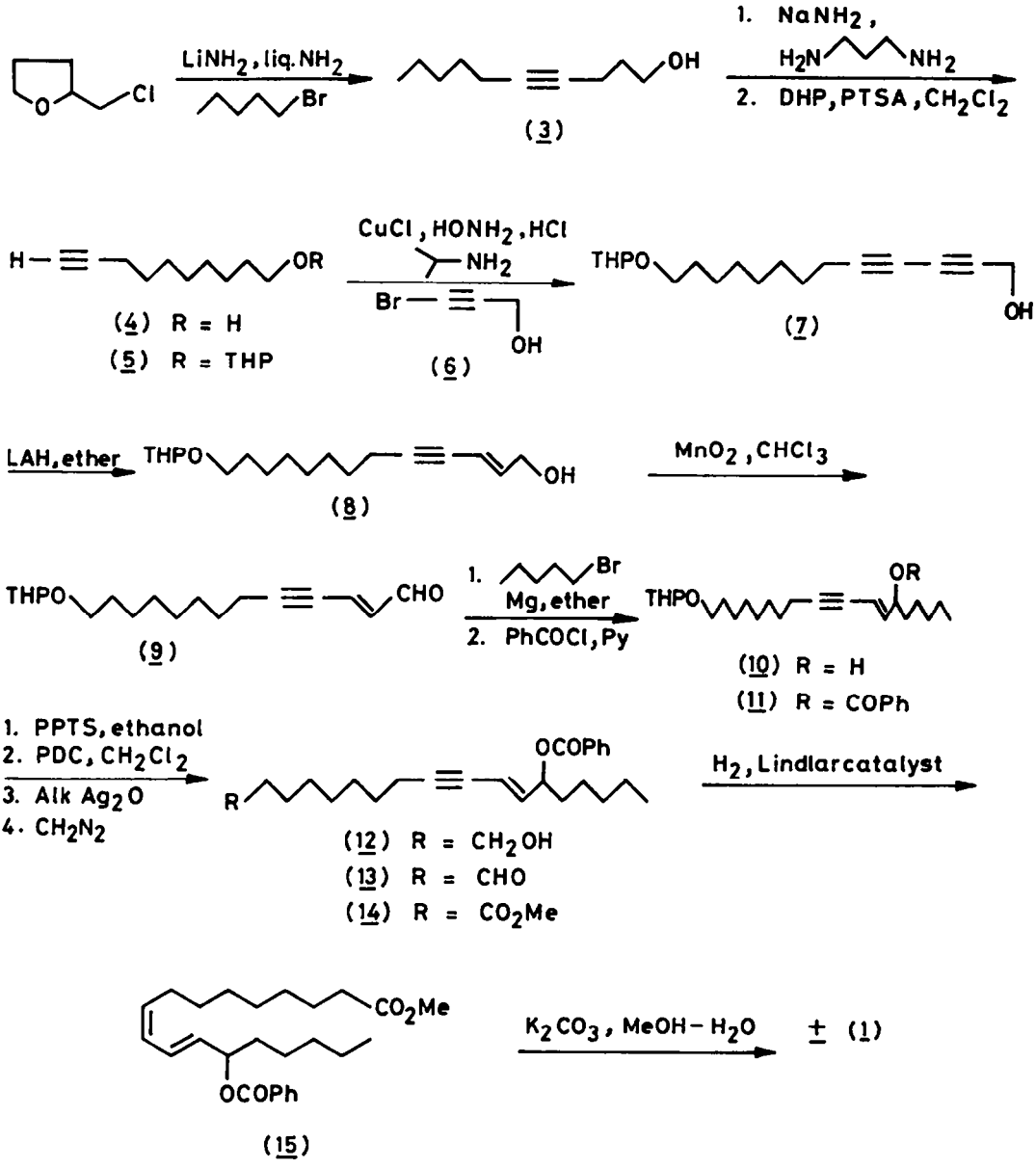
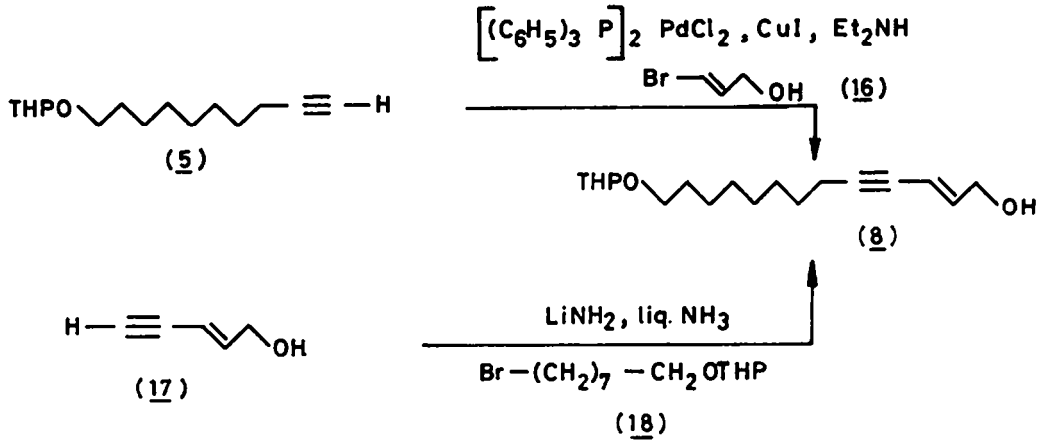
Scheme 1



methane to afford the ester 14 in 70% overall yield. Partial hydrogenation of acetylenic bond in 14 using Lindlar catalyst in presence of quinoline yielded methyl(9Z,11E)-13-benzoyl oxyoctadecadienoate (15) in 89% yield. Saponification of 15 with K_2CO_3 in aqueous methanol afforded coriolic acid 1 in 65% yield after chromatographic purification.

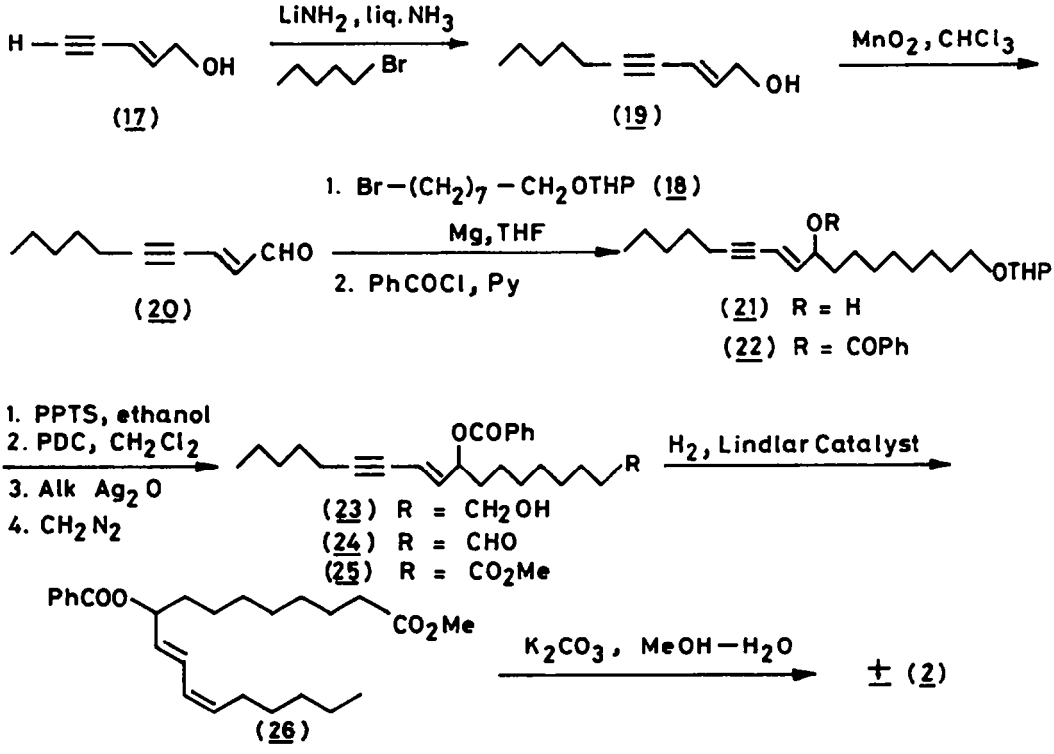
The key intermediate 8 in the synthesis of coriolic acid (1) was also prepared (Scheme 2) by two other approaches. Sonayashira reaction of the THP ether of 9-decyn-1-ol 5 with (E)-3-bromoprop-2-en-1-ol (16)[16] in presence of cuprous iodide and bis (triphenylphosphine) palladium(II)chloride in diethylamine gave 8 in 72% yield. Alternatively 8 was also made by alkylation of (E)-pent-2-en-4-yn-1-ol (17)[17] with tetrahydropyranyl ether of 8-bromo-1-octanol (18) in the presence of lithium amide in liquid ammonia in 70% yield.

Scheme 2



The strategy for the synthesis of dimorphecolic acid (2) mainly centers round (E)-pent-2-en-4-yn-1-ol (17) which should facilitate for the elaboration of the aliphatic chain as desired and allows the acetylenic bond in the alcohol to serve as precursor for the cis double bond.

Scheme 3



Thus, alkylation of 17 (Scheme 3) with n-pentyl bromide using lithium amide in liquid ammonia gave 19 in 68% yield. Oxidation of 19 with active manganese dioxide in chloroform afforded aldehyde 20 in 85% yield which on Grignard reaction with 18 in THF afforded the alcohol 21 in 55% yield. The secondary alcohol in 21 was protected by benzoylation to give 22 in 83% yield which on depyranylation using PPTS in ethanol gave the benzoate-alcohol (23) in 75% yield. Step-wise oxidation of alcohol 23 with PDC gave the corresponding aldehyde 24 which on alkaline silver oxide oxidation and esterification of the resulting acid with etherial diazomethane gave the methyl ester 25 in 70% overall yield. Partial

reduction of 25 was carried out by hydrogenation using Lindlar catalyst to yield methyl (10E,12Z)-9-benzoyloxy octadecadienoate 26 in 90% yield. Saponification of 26 using K_2CO_3 in aqueous methanol and chromatographic purification afforded dimorphecolic acid in 65% yield.

Experimental

IR spectra (ν_{max} in cm^{-1}) were recorded in nujol or neat on a Perkin Elmer Model 683 spectrometer with sodium chloride optics. ^{1}H-NMR spectra were obtained on Varian T-60 or Varian FT-80 or Bruker WH-90 spectrometer in $CDCl_3$ or CCl_4 solutions containing TMS as an internal standard with chemical shifts (δ) expressed in PPM down field from TMS. Mass spectra were run on AEI MS 30 double beam mass spectrometer or CEC 21-110 B spectrometer. All solvents and reagents were purified and dried by standard techniques. Column chromatography was performed using silica gel (60-120 mesh Acme). Progress of the reactions was checked by TLC on 0.2 mm layers of silica gel using iodine chamber for visualisation.

3-Bromo-2-propyn-1-ol (6) : It was made from propargyl alcohol according to the reported procedure[11].

(E)-3-Bromo-prop-2-en-1-ol (16) : It was made from 3-bromo-2-propyn-1-ol (6) according to reported procedure[16].

(E)-Pent-2-en-4-yn-1-ol (17) : It was prepared according to the reported procedure[17].

8-[(Tetrahydro-2H-pyran-2-yl)-oxy] octane-1-ol (18)

Octane-1,8-diol (14.6 g, 0.1 mol) was refluxed with 48% hydrobromic acid (18.5 ml) in toluene for 6 hr. The cooled reaction mixture was diluted with water and the organic layer was washed with 10% aqueous $NaHCO_3$ solution, brine and dried (Na_2SO_4). The solvent was evaporated to give 8-bromo-octanol (14.63 g) in 70% yield.

8-Bromooctanol (14.63 g, 0.07 mol) dihydropyran (7.64 g, 0.091 mol) and p-toluenesulfonic acid (0.15 g) were stirred in dry dichloromethane (130 ml) at room temperature for 3 hr. The reaction mixture was diluted with dichloromethane, washed with 5% aqueous $NaHCO_3$ and dried (Na_2SO_4). Evaporation of the solvent and chromatographic purification (silica gel) of the residue gave the THP-ether (18) (18.45 g) in 90% yield.

4-Decyn-1-ol (3)

To a freshly prepared suspension of lithium amide (prepared from 4.2 g, 0.6 mol of lithium) in liquid ammonia (400 ml) was added 2-chloromethyl tetrahydrofuran (24 g, 0.2 mol) over a period of 15 min. The reaction mixture was stirred for 3 hr at -33°, then a solution of n-pentylbromide (30.2 g, 0.2 mol) in THF (40 ml) was added slowly and allowed for an additional 30 min. Ammonia was allowed to evaporate and quenched the reaction with 20% aqueous ammonium chloride. It was extracted with ether, washed with brine and dried (Na_2SO_4). Evaporation of the solvent and distillation of the resulting residue gave (3) (18.4 g) in 60% yield. b.p. 90-91°/1 mm (Lit.[18] b.p. 85-86°/0.05 mm).

9-Decyn-1-ol (4)

A suspension of sodium amide (3.51 g, 0.09 mol) in 1,3-diaminopropane (48 ml) was heated at 80° for 25 min. It was cooled to room temperature and 3 (4.62 g, 0.03 mol) was added to the stirred suspension during 15 min. The reaction mixture was heated at 80° for 2 hr. It was cooled and cold water (300 ml) was added and extracted with ether. The organic layer was washed with water, 5% hydrochloric acid, brine and dried (Na_2SO_4). The solvent was removed and the residue was purified by chromatography (silica gel) to afford 4 (3.92 g) in 85% yield.

IR : 2140 cm^{-1} (C≡C) and 3450 cm^{-1} (OH and C≡C-H). ^{1}H-NMR (CCl_4) : δ 1.1-1.6 (m, 12H, 6 x $-CH_2-$), 1.73 (t, 1H, -C≡C-H), 2.03 (dist. t, 2H, -C≡C-CH_2), 3.46 (t, 3H, -CH_2OH and -OH).

1-[(Tetrahydro-2H-pyran-2-yl)-oxy]-9-decyne (5)

A mixture of alcohol (4, 3.0 g, 19.5 m.mol), dihydropyran (3 ml, 30 m.mol) and p-toluene sulfonic acid (0.10 g) was stirred in dry dichloromethane (40 ml) at room temperature for 6 hr. The reaction mixture was diluted with dichloromethane, washed with 5% aqueous sodium bicarbonate dried, (K_2CO_3). Evaporation of the solvent and chromatographic purification (silica gel) of the residue gave 5 (3.93 g) in 85% yield as pale yellow oil[19].

IR : 2140 cm^{-1} (C≡C) and 3450 cm^{-1} (C≡C-H). ^{1}H-NMR (CCl_4) : δ 1.16-1.66 (m, 18H, 9 x $-CH_2-$), 1.76 (t, 1H, -C≡C-H), 2.13 (dist. t, 2H, -C≡C-CH_2), 3.10-4.00 (m, 4H, 2 x $-OCH_2-$), 4.46 (br, s, 1H, 3°H).

13-[(Tetrahydro-2H-pyran-2-yl)-oxy]-2,4-tridecadiyn-1-ol (7)

A mixture of 5 (3.57g, 15 m.mol), freshly prepared cuprous chloride powder (0.040 g), 33% methanolic isopropyl amine (5.6 ml) and hydroxylamine hydrochloride (0.040 g) in methanol (45 ml) was treated with 3-bromo-2-propyn-1-ol (6) (2.53 g, 18.75 m.mol) with stirring during 1 hr. Small amounts of hydroxylamine hydrochloride were added to discharge the green colour which developed. A solution of potassium cyanide (0.1 g) in water (20 ml) was added. The aqueous layer was extracted with ether (4 x 25 ml), dried (Na_2SO_4) and concentrated. The residue thus obtained was purified by chromatography (silica gel) to give 7 (3.5 g) in 80% yield.

IR : 2260 cm^{-1} (C≡C-C≡C) and 3440 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) : δ 1.23-1.76 (m, 18H, 9 x $-CH_2-$), 2.26 (dist. t, 2H, -C≡C-CH_2-), 3.20-3.93 (m, 4H, 2 x $-OCH_2-$), 4.26 (S, 2H, -CH_2OH), 4.53 (br,s, 1H, 3°H). M^+ 292. Analysis calculated for $C_{18}H_{28}O_3$: C, 73.97; H, 9.60; Found : C, 74.05; H, 9.57%.

(E)-13-[(Tetrahydro-2H-pyran-2-yl)-oxy]-tridec-2-en-4-yn-1-ol (8)

Method 1

To a stirred suspension of LAH (0.19 g, 5 m.mol) in ether (10 ml), a solution of 7 (1.46 g, 5 m.mol) in ether (5 ml) was added at 0° and the reaction mixture was then stirred at room temperature for 3 hr. It was quenched with ice cold water and extracted with ether. The organic layer was washed with water, brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 8 (1.47 g) in quantitative yield.

IR : 960 cm^{-1} (trans -HC=CH-), 2220 cm^{-1} (C≡C) and 3340 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) : δ 1.05-1.90 (m, 18H, 9 x $-CH_2-$), 2.10-2.50 (m, 2H, -C≡C-CH_2-), 3.20-4.00 (m, 4H, 2 x $-OCH_2-$), 4.15 (d, 2H, -CH_2OH), 4.55 (br. s, 1H, 3°H), 5.45-6.32 (m, 2H, olefinic). M^+ 294. Analysis calculated for $C_{18}H_{30}O_3$: C, 73.46; H, 10.20; Found : C, 73.40; H, 10.30%.

Method 2

A stirred mixture of 5 (0.476 g, 2 m.mol) cuprous iodide (0.008 g, 0.04 m.mol) bis(triphenylphosphine) palladium(II)chloride (0.007 g, 0.01 m.mol) in diethylamine (10 ml) was treated with (E)-3-bromoprop-2-en-1-ol (16) (0.356 g, 2.6 m.mol) at 40°. After 6 hr, solvent was removed and the residue was purified by chromatography (silica gel) to give the alcohol 8 (0.423 g) in 72% yield. It was identical in all respects with the sample prepared in the earlier method.

Method 3

To a freshly prepared suspension of lithium amide (prepared from 0.97 g, 0.138 g atom of lithium) in liquid ammonia (140 ml) were added acetylenic alcohol 17 (5.68 g, 0.0698 mol) in THF (15 ml) during

15 min and bromide 18 (18.46 g, 0.063 mol) in THF (20 ml) during 30 min. After the addition the reaction mixture was stirred for further 4 hr at -33° and then quenched by portion-wise addition of ammonium chloride (20 g). The ammonia was then allowed to evaporate. The residue was dissolved in water and extracted with ether. The combined ethereal extract was washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent and chromatographic purification (silica gel) afforded 8 (12.96 g) in 70% yield which was identical in all respects with the sample prepared in the earlier methods.

(E)-13-[(Tetrahydro-2H-pyran-2-yl)-oxy]-tridec-2-en-4-yn-1-al (9)

To a solution of 8 (1.47 g, 5 m.mol) in chloroform (60 ml), active manganese dioxide (15 g) was added and stirred at room temperature for 5 hr. The reaction mixture was filtered and concentrated to give the aldehyde 9 (1.3 g) in 89% yield.

IR : 1710 cm^{-1} (C=O) and 2220 cm^{-1} (-C≡C-). ^{1}H-NMR ($CDCl_3$) : δ 1.26-1.83 (m, 18H, 9 x $-CH_2-$), 2.46 (dist. t, 2H, $-C\equiv C-CH_2-$), 3.20-3.96 (m, 4H, 2 x $-OCH_2-$), 4.56 (br.s, 1H, 3°H), 6.23-6.53 (m, 2H, olefinic). M^+ 292. Analysis calculated for $C_{18}H_{28}O_3$: C, 73.97; H, 9.60: Found : C, 73.89; H, 9.60%.

(E)-18-[(Tetrahydro-2H-pyran-2-yl)-oxy]-octadec-7-en-9-yn-6-ol (10)

A solution of n-pentyl bromide (0.9 g, 6 m.mol) in dry ether (5 ml) was added to magnesium (0.15 g, 0.006 g atom) in ether (3 ml) over a period of 15 min.at room temperature under nitrogen atmosphere. After 1 hr, a solution of aldehyde (11, 1.16 g, 3.97 m.mol) in THF (10 ml) was added drop-wise and allowed to stir for further 1 hr. The mixture was poured into ice cold aqueous ammonium chloride solution and extracted with ether (3 x 20 ml). The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give 10 (1.0 g) in 69% yield.

IR : 2210 cm^{-1} (-C≡C-) and 3450 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$): δ 0.93 (dist. t, 3H, $-CH_3$), 1.16-1.73 (m, 26H, 13 x $-CH_2-$), 2.21 (dist. t, 2H, $-C\equiv C-CH_2-$), 3.16-3.73 (m, 4H, 2 x $-OCH_2-$), 3.83-4.08 (m, 1H, -CHOH), 4.43 (br. s , 1H, 3°H), 5.20-5.80 (m, 2H, Olefinic). M^+ 364. Analysis calculated for $C_{23}H_{40}O_3$ C, 75.82; H, 10.98 : Found C, 75.61; H, 10.92%.

(E)-13-Benzoyloxy-1 [(tetrahydro-2H-pyran-2-yl)-oxy]-octadec-11-en-9-yne (11)

Benzoyl chloride (0.5 g, 3.57 m.mol) was added drop-wise with stirring at O° to a solution of the alcohol 10 (0.91 g, 2.5 m.mol) in dry pyridine (10 ml) during 10 min. The reaction was allowed to warm to room temperature and stirred for further 6 hr. It was quenched with ice cold water and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed successively with water, 5% cold hydrochloric acid, 5% aqueous $NaHCO_3$ and brine, dried (Na_2SO_4). Evaporation of the solvent furnished the benzoate 11 (0.994 g) in 85% yield.

IR : 1720 cm^{-1} (C=O), 2200 cm^{-1} (C≡C). ^{1}H-NMR ($CDCl_3$) : δ 0.90 (dist. t, 3H, $-CH_3$), 1.15-1.75 (m, 26H, 13 x $-CH_2-$), 2.25 (dist. t, 2H, $-C\equiv C-CH_2-$), 3.30-3.90 (m, 4H, 2 x $-OCH_2-$), 4.55 (br. s, 1H, 3°H), 5.45 (q, 1H, CHOBz), 5.60-6.15 (m, 2H, olefinic), 7.25-7.50 (m, 3H, Ar, -H), 7.90-8.05 (m, 2H, Ar, -H); M^+ 468. Analysis calculated for $C_{30}H_{44}O_4$: C, 76.92; H, 9.40 : Found : C, 769 0; H, 9.32 %.

(E)-13-Benzoyloxy octadec-11-en-9-yn-1-ol (12)

A solution of the benzoate 11 (0.936 g, 2 m.mol) in ethanol (10 ml) containing PPTS (0.020 g) was stirred at 55° for 2 hr. Ethanol was removed, the residue was treated with ether and decanted. The combined ethereal layer was evaporated and the residue obtained was purified by column chromatography (silica gel) to afford 12 (0.6 g) in 78% yield.

IR : 1720 cm^{-1} (C=O), 2220 cm^{-1} (-C≡C-) and 3350 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) : δ 0.90 (dist. t, 3H, $-CH_3$), 1.15-1.80 (m, 20H, 10 x $-CH_2-$), 2.25 (br. s , 3H, $-C\equiv C-CH_2$ and OH), 3.62 (t, 2H, $-CH_2OH$), 5.45 (q, 1H, CHOBz), 5.65-6.25 (m, 2H, olefinic), 7.25-7.55 (m, 3H, Ar-H), 7.95-8.15 (m, 2H, Ar-H). M^+ 384. Analysis calculated for $C_{25}H_{36}O_3$: C, 78.12; H, 9.37 : Found : C, 77.98; H, 9.28 %.

(E)-13-Benzoyloxyoctadec-11-en-9-yn-1-al (13)

To a stirred suspension of pyridinium dichromate (1.12 g, 3 m.mol) in dichloromethane (30 ml) was added a solution of the alcohol 12 (0.576 g, 1.5 m.mol) in dichloromethane (15 ml) at room temperature. After a period of 6 hr the reaction mixture was treated with ether and filtered over silica gel. The filtrate was concentrated to afford 13 (0.429 g) in 75% yield.

IR : 1720 cm^{-1} (br. C=O) and 2220 cm^{-1} (-C≡C-). ^{1}H-NMR ($CDCl_3$) : δ 0.86 dist. t, 3H, $-CH_3$), 1.15-1.65 (m, 18H, 9 x CH_2-), 2.15-2.55 (m, 4H, $-C\equiv CCH_2-$ and $-CH_2CHO$), 5.45 (q, 1H, -CHOBz), 5.70-6.20 (m, 2H, olefinic), 7.25-7.55 (m, 3H, Ar-H), 7.95-8.10 (m, 2H, Ar-H), 9.75 (s, 1H, -CHO); M^+ 382. Analysis calculated for $C_{25}H_{34}O_3$: C, 78.53; H, 8.90; Found : C, 78.50; H, 8.87%.

Methyl (E)-13-benzoyloxy-11-en-9-yn-octadecadienoate (14)

To a solution of the aldehyde 13 (0.382 g, 1 m.mol) in ethanol (5 ml) was added successively a solution of silver nitrate (0.170 g, 1 m.mol) in water (3 ml) followed by potassium hydroxide (0.112-g, 2 m.mol) in water (3 ml) drop wise. The reaction mixture was stirred for 2 hr at room temperature and filtered. The filtrate was neutralised with 5% HCl and extracted with ether. The ethereal layer was washed with water, brine, dried (Na_2SO_4) and on evaporation afforded crude acid which was treated with ethereal diazomethane at 0° and allowed it for 30min.Evaporation of the solvent and chromatographic (silica gel) purification afforded ester 14 (0.305 g) in 70% yield.

IR : 1720 and 1740 cm^{-1} (C=O) : 2200 cm^{-1} (C≡C). ^{1}H-NMR ($CDCl_3$) : δ 0.85 (dist. t, 3H, $-CH_3$), 1.15-1.85 (m, 18H, 9 x $-CH_2$-), 2.30 (t, 4H, $-C\equiv C-CH_2-$ and $-CH_2CO_2Me$), 3.65 (s, 3H, $-OCH_3$), 5.50 (q, 1H, CHOBz), 5.65-6.20 (m, 2H, olefinic), 7.25-7.60 (m, 3H, Ar-H), 7.95-8.15 (m, 2H, Ar-H). M^+ 412. Analysis calculated for $C_{26}H_{36}O_4$: C, 75.72; H, 8.73; Found : C, 75.63; H, 8.70%.

Methyl (9Z,11E)-13-benzoyloxy octadecadienoate (15)

A mixture of the ester 14 (0.123 g, 0.3 m.mol) and Lindlar's catalyst (0.030 g) in hexane (10 ml) containing 2 drops of quinoline was subjected to hydrogenation at atmospheric pressure. After the absorption of required amount of hydrogen (6.6 ml) the suspension was filtered and washed with hexane. The hexane layer was washed with water, dried (Na_2SO_4) and evaporated. The residue obtained was purified by chromatography (silica gel) to give 15 (0.11 g) in 89% yield.

IR : 1720 cm^{-1} (C=O), 725 and 960 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.85 (t, 3H, $-CH_3$), 1.10-1.85 (m, 18H, 9 x CH_2-), 2.00-2.40 (m, 4H, $C\equiv C-CH_2$ and CH_2CO_2Me), 3.65 (s, 3H, $-OCH_3$), 5.25-6.15 (m, 5H, olefinic and 3°H), 7.30-7.60 (m, 3H, Ar-H), 7.95-8.15 (m, 2H, Ar-H). M^+ 414. ^{13}C-NMR ($CDCl_3$)[4]: δ 174.56, 134.00, 131.34, 128.61, 127.96, 75.64, 34.89, 34.31, 31.84, 29.70, 29.57, 29.31, 29.15, 29.15, 28.01, 25.15, 22.74 and 14.16. Chemical shifts of benzoate group and methyl of methyl ester were omitted. Analysis calculated for $C_{26}H_{38}O_4$: C, 75.36; H, 9.17; Found : C, 75.29; H, 9.20%.

13-Hydroxy-9Z,11E-octadeca dienoic acid (coriolic acid) (1)

A mixture of ester 15 (0.103 g, 0.25 m.mol) and K_2CO_3 (0.207 g, 1.5 m.mol) in aqueous methanol (5 ml, 4:1) was stirred at room temperature for 12 hr. It was diluted with water carefully acidified with 5% methanolic acetic acid and extracted with ether. Ethereal solution was washed with water, dried (Na_2SO_4) and evaporated. The residue obtained was purified by chromatography (silica gel) to afford 1 (0.48 g) in 65% yield.

IR : 1700 cm^{-1} (C=O), 3350 cm^{-1} (OH and COOH). ^{1}H-NMR ($CDCl_3$) : δ 0.9 (dist. t, 3H, $-CH_3$), 1.2-1.8 (m, 18H, 9 x $-CH_2$-), 2.1-2.4 (m, 4H, $C\equiv C-CH_2-$ and CH_2-CO_2Me), 4.1 (m, 1H, CHOH), 5.5-6.3 (m, 4H, olefinic). M^+ 296. Analysis calculated for $C_{18}H_{32}O_3$: C, 72.98; H, 10.81; Found : C, 72.90; H, 10.79%.

(E)-dec-2-en-4-yn-1-ol (19)

To a freshly prepared suspension of lithium amide (prepared from 0.7 g, 0.1 mol of lithium) in liquid ammonia (100 ml) was added acetylene alcohol 17 (4.1 g, 0.05 mol) over a period of 15 min. Then a solution of n-pentyl bromide (7.55 g, 0.05 mol) in THF (15 ml) was added slowly and stirred for 4 hr at -33°. Ammonia was allowed to evaporate and quenched the reaction with 20% aqueous ammonium chloride. It was extracted with ether, washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent and chromatographic purification (silica gel) afforded 19 (5.23 g) in 68% yield.

IR : 2220 cm^{-1} (-C≡C-) and 3450 cm^{-1} (OH). ^{1}H-NMR (CCl_4) : δ 0.9 (dist. t, 3H, $-CH_3$), 1.2-1.7 (m, 6H, 3 x $-CH_2-$), 2.2-2.5 (m, 2H, $-C\equiv C-CH_2-$), 4.1 (d, 2H, CH_2OH), 5.4-6.3 (m, 2H, olefinic). M^+-152. Analysis calculated for $C_{10}H_{16}O$: C, 78.96; H, 10.53; Found : C, 78.81; H, 10.46%.

(E)-Dec-2-en-4-yn-1-al (20)

To a solution of 19 (3.04 g, 0.02 mol) in chloroform (120 ml), active manganese dioxide (30 g) was added and stirred at room temperature for 4 hr. The reaction mixture was filtered and on concentration gave the aldehyde 20 (2.56 g) in 85% yield.

IR : 2220 cm^{-1} (-C≡C-) and 1710 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) : δ 0.9 (dist. t, 3H, $-CH_3$), 1.2-1.75 (m, 6H, 3 x $-CH_2-$), 2.3-2.6 (m, 2H, $-C\equiv C-CH_2-$), 6.4-6.6 (m, 2H, olefinic), 9.9 (dd, 1H, -CHO). M^+ 150. Analysis calculated for $C_{10}H_{14}O$: C, 80.54; H, 8.72; Found : C, 80.46; H, 8.61%.

(E)-1-[(Tetrahydro-2H-pyran-2-yl)oxy] octadec-10-en-12-yn-9-ol (21)

A solution of 18 (2.93 g, 10 m.mol) in THF (5 ml) was added to magnesium (0.25 g, 0.01 g.atom) in ether (3 ml) over a period of 10 min. under nitrogen atmosphere and was refluxed for 4 hr. Then to the cooled reaction mixture, a solution of aldehyde 20 (0.750 g, 5 m.mol) in THF (3 ml) was added and stirred for 6 hr at room temperature. The reaction mixture was quenched with aqueous ammonium chloride and extracted with ether. The etherial layer was washed with water, dried (Na_2SO_4) and was purified by chromatography (silica gel) to give the alcohol 21 (1.02 g) in 55% yield.

IR : 2220 cm^{-1} (-C≡C-) and 3450 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) : δ 0.93 (dist. t, 3H, $-CH_3$), 1.15-1.75 (m, 26H, 13 x $-CH_2-$), 2.22 (dist. t, 2H, $-C\equiv C-CH_2-$), 3.15-3.72 (m, 4H, 2 x $-OCH_2-$), 3.83-4.08 (m, 1H, -CHOH), 4.43 (br. s, 1H, 3°H), 5.2-5.81 (m, 2H, olefinic). M^+ 364. Analysis calculated for $C_{23}H_{40}O_3$: C, 75.82; H, 10.98 ; Found : C, 75.71; H, 10.91%.

(E)-9-Benzoyloxy-1-[(tetrahydro-2H-pyran-2-yl)oxy] octadeca-10-en-12-yn (22)

Benzoyl chloride (0.5 g, 3.57 m.mol) was added drop wise with stirring at 0° to a solution of 21 (0.91 g, 2.5 m.mol) in dry pyridine during 10 min. and followed the procedure given in the preparation of 11 to give the compound 22 (0.990 g) in 83% yield.

IR : 1720 cm^{-1} (C=O) and 2220 cm^{-1} (-C≡C-). ^{1}H-NMR ($CDCl_3$) : δ 0.90 (dist. t, 3H, $-CH_3$), 1.2-1.75 (m, 26H, 13 x $-CH_2-$), 2.25 (dist. t, 2H, $-C\equiv C-CH_2-$), 3.3-3.9 (m, 4H, 2 x $-OCH_2-$), 4.53 (br. s, 1H, 3°H), 5.46 (q, 1H, CHOBz), 5.5-6.2 (m, 2H, olefinic), 7.25-7.5 (m, 3H, Ar-H), 7.90-8.05 (m, 2H, Ar-H). M^+ 468. Analysis calculated for $C_{30}H_{44}O_4$: C, 76.92; H, 9.40; Found : C, 76,90; H, 9.32%.

(E)-9-Benzoyloxy octadec-10-en-12-yn-1-ol (23)

A solution of the benzoate 22 (0.936 g, 2 m. mol) in ethanol (15 ml) containing PPTS (0.025 g) was stirred at 55° for 2 hr. Ethanol was removed, the residue was treated with ether. The ethereal layer was evaporated and residue obtained was purified by column chromatography (silica gel) to afford 23 (0.58 g) in 75% yield.

IR : 1720 cm^{-1} (C=O), 2220 cm^{-1} (-C≡C-) and 3350 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) : δ 0.09 (dist. t, 3H, $-CH_3$), 1.15-1.75 (m, 20H, 10 x $-CH_2-$), 2.0 (s, 1H, OH), 2.2-2.4 (m, 2H, $-C\equiv C-CH_2-$), 3.68 (t, 2H,

2H, -C<u>H</u>$_2$OH), 5.47 (q, 1H, C<u>H</u>OBz), 5.5-6.25 (m, 2H, olefinic), 7.25-7.55 (m, 3H, Ar-H), 7.95-8.16 (m, 2H, Ar-H). M^+ 384. Analysis calculated for $C_{25}H_{36}O_3$: C, 78.12; H, 9.37; Found : C, 77.91; H, 9.28%.

<u>(E)-9-Benzoyloxy octadec-10-en-12-yn-1-al (24)</u>

To a stirred suspension of pyridinium dichromate (1.12 g, 3 mol) in dry dichloromethane (35 ml) was added a solution of the alcohol <u>23</u> (0.57 g, 1.5 m.mol) in dichloromethane (10 ml) at room temperature. After a period of 6 hr the reaction mixture was treated with absolute ether and filtered. The filtrate was concentrated to afford <u>24</u> (0.42 g) in 71% yield.

IR : 1720 cm^{-1} (br. C=O) and 2210 cm^{-1} (-C≡C-). ^{1}H-NMR ($CDCl_3$) : δ 0.88 (dist. t, 3H, -CH_3), 1.15-1.70 (m, 18H, 9 x -CH_2-), 2.20-2.55 (m, 4H, -C≡C-CH_2 and -C<u>H</u>$_2$CHO), 5.47 (q, 1H, C<u>H</u>OBz), 5.6-6.25 (m, 2H, olefinic), 7.25-7.55 (m, 3H, Ar-H), 7.95-8.10 (m, 2H, Ar-H), 9.75 (s, 1H, -CHO). Analysis calculated for $C_{25}H_{34}O_3$: C, 78.53; H, 8.90; Found : C, 78.50, H, 8.87%.

<u>Methyl (E)-9-benzoyloxy-10-en-12-yn-octadeca dienoate (25)</u>

To a solution of aldehyde <u>24</u> (0.381 g, 1 m.mol) in ethanol (5 ml) was added successively a solution of silver nitrate (0.170 g, 1 m.mol) in water (4 ml) followed by potassium hydroxide (0.0113 g, 2 m.mol) in water (3 ml) drop wise and followed the same procedure adopted for compound <u>14</u> to give crude acid which was esterified by using diazomethane to afford the ester <u>25</u> (0.35 g) in 70% yield.

IR : 1720 and 1740 cm^{-1} (C=O), 2210 cm^{-1} (-C≡C-). ^{1}H-NMR ($CDCl_3$) : δ 0.85 (dist.t, 3H, -CH_3), 1.15-1.80 (m, 18H, 9 x -CH_2-), 2.30 (t, 4H, -C≡C-CH_2 and C<u>H</u>$_2$$CO_2$Me), 3.65 (s, 3H, -$OCH_3$), 5.48 (q, 1H, C<u>H</u>OBz), 5.60-6.25 (m, 2H, olefinic), 7.25-7.60 (m, 3H, Ar-H), 7.95-8.15 (m, 2H, Ar-H). M^+ 412. Analysis calculated for $C_{26}H_{36}O_4$: C, 75.72; H, 8.73; Found : C, 75.62; H, 8.74%.

<u>Methyl (10E, 12Z)-9-benzoyloxy octadeca dienoate (26)</u>

A mixture of the <u>25</u> (0.206 g, 0.5 m.mol) and Lindlar's catalyst (0.050 g) in hexane (15 ml) containing 2 drops of quinoline was subjected to hydrogenation at atmospheric pressure. After the absorption of required amount of hydrogen, the suspension was filtered, washed with water, dried (Na_2SO_4) and evaporated. The residue obtained was purified by chromatography (silica gel) to give <u>26</u> (0.186 g) in 90% yield.

IR : 1720 cm^{-1} (C=O), 725 and 960 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 0.85 (t, 3H, -CH_3), 1.15-1.85 (m, 18H, 9 x -CH_2-), 2.00-2.40 (m, 4H, -C=C-CH_2 and -C<u>H</u>$_2$$CO_2$Me), 3.7 (s, 3H, -$OCH_3$), 5.25-6.25 (m, 5H, olefinic and 3°H), 7.3-7.60 (m, 3H, Ar-H), 7.95-8.15 (m, 2H, Ar-H). M^+ 414. ^{13}C-NMR ($CDCl_3$)[4] δ 174.46, 134.00, 131.24, 128.60, 127.70, 75.54, 34.88, 34.30, 31.50, 29.71, 29.57, 29.10, 29.1, 27.65, 25.00, 24.80, 22.40 and 14.16. Chemical shifts of benzoate group and methyl of methyl ester were omitted. Analysis calculated for $C_{26}H_{38}O_4$: C, 75.36; H, 9.17; Found : C, 75.27; H, 9.21%.

<u>9-Hydroxy-10E,12Z-octadeca dienoic acid (dimorphecolic acid) (2)</u>

A mixture of ester <u>26</u> (0.103 g, 0.25 m.mol) and K_2CO_3 (0.207 g, 1.5 m.mol) in aqueous methanol (10 ml, 8:2) was stirred at room temperature for 12 hr and followed the procedure adopted for <u>1</u> to give <u>2</u> (0.96 g) in 65% yield.

IR : 1700 cm^{-1} (C=O) and 3350 cm^{-1} (OH and COOH). ^{1}H-NMR ($CDCl_3$) : δ 0.9 (dist. t, 3H, -CH_3), 1.2-1.78 (m, 18H, 9 x -CH_2-), 2.1-2.4 (m, 4H, -C=C-CH_2 and C<u>H</u>$_2$-CO_2H), 4.12 (m, 1H, C<u>H</u>OH), 5.5-6.3 (m, 4H, olefinic). M^+ 296. Analysis calculated for $C_{18}H_{32}O_3$: C, 72.98; H, 10.81; Found : C, 72.89, H, 10.77%.

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