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A STEREOSELECTIVE SYNTHESIS OF CORIOLIC ACID AND DIMORPHECOLIC ACID

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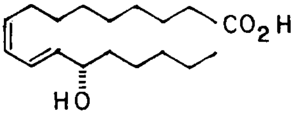
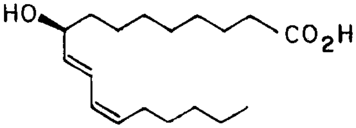
Described herein is a convenient synthesis of coriolic acid (1) and dimorphecolic acid (2), the two natural ionophores derived respectively from bovine heart mitochondria and also shown to be self defensive substances in rice plant against rice blast disease.

Coriolic acid (1)[1] and dimorphecolic acid (2)[2] earlier isolated from bovine heart mitochondria[3], belong to a family of oxyoctadecadienoate congeners and commonly found in vegetable oils are shown to possess unique calcium specific ionophoric activity[4]. Recently both these products have been isolated from the resistant cultivar of rice plant, (Oryza sativa L.) and demonstrated to act as self defensive substances against rice blast disease[5]. These findings prompted us to accomplish their total synthesis by a convenient approach so that their biological properties can be well assessed.



(1)



(2)

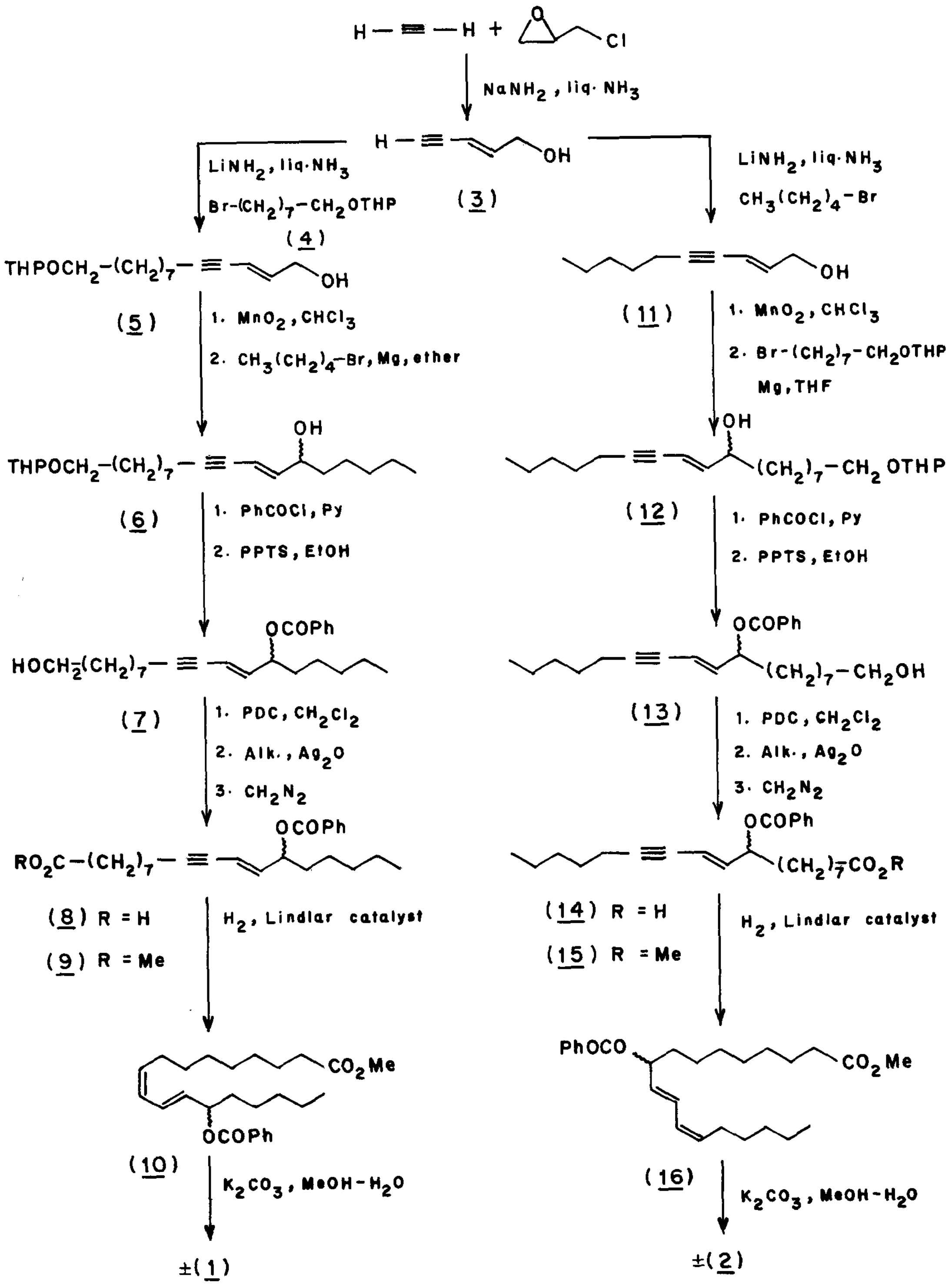
Our strategy for the synthesis of 1 and 2 centers round (E)-2-pentene-4-yn-1-ol (3) which should facilitate for the elaboration of the aliphatic chain as desired and allow the acetylenic bond to serve as a precursor for the cis double bond.

The key synthon, (E)-pent-2-ene-4-yn-1-ol (3) was made[6] by treating excess acetylene with epichlorohydrin and sodamide in liquid ammonia at -32° for 3 hr and usual work up. Alkylation of 3 with tetrahydropyranyl ether of 8-bromo-1-octanol (4, $LiNH_2$, liq.NH_3, -32°, 4 hr) gave 5[7] in 70% yield. Compound 5 not only possesses strategically situated oxygen functionalities for the eventual elaboration of the aliphatic chain but also allows the introduction of the carboxyl group during the penultimate stage of the synthetic sequences. 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 intermediate (5) was also made by two different approaches[8]. Oxidation of 5 with activated MnO_2 in $CHCl_3$ furnished the corresponding aldehyde which was treated with n-pentyl magnesium bromide in ether to obtain the alcohol (6) in 60% yield from 5. The secondary alcohol in 6 was protected by benzoylation (PhCOCl, pyridine, 25°, 6 hr) and later subjected to depyranylation (pyridinium-p-toluene sulphonate[9], EtOH, 55°, 2 hr) to give the alcohol (7) in 78% yield from 6. Direct oxidation of 7 as well as its THP ether with Jones reagent led to a complex mixture of products. However, stepwise oxidation of the alcohol 7 with pyridinium dichromate in CH_2Cl_2 resulted in the formation of the corresponding aldehyde which was directly subjected to alkaline silver oxide oxidation ($AgNO_3$, 15% KOH, H_2O) to give the acid 8 in 70% overall yield. Esterification of 8 with ethereal CH_2N_2 gave the ester 9 in almost quantitative yield. Partial hydrogenation of the acetylenic bond to yield the single diolefinic ester 10 was carried out using Lindlar catalyst in presence of quinoline. The PMR and ^{13}C NMR of 10 were in full agreement with the reported[5] values of the benzoate of methyl ester of 13-hydroxy-(Z)-9-(E)-11-octadecadienoic acid. Saponification of 10 with 3 eq. of K_2CO_3 in 25% aqueous MeOH (25°. 12 hr) followed by careful acidification with methanolic acetic acid afforded coriolic acid (1) in 65% yield after silica gel chromatographic purification.

Synthesis of dimorphecolic acid (2) was also achieved by a similar sequence of reactions (Scheme 1) starting from (E)-pent-2-ene-4-yn-1-ol (3). Thus alkylation of 3 with n-amyl bromide ($LiNH_2$, Liq.NH_3, -32°, 4 hr) gave 11 in 74% yield. Oxidation of 11 with MnO_2 in $CHCl_3$ followed by Grignard reaction of the aldehyde with 4 in THF afforded the alcohol (12) in 65% yield from 11. Protection of the secondary alcohol in 12 by benzoylation followed by depyranylation gave the benzoate alcohol (13) in 80% overall yield. Stepwise oxidation of the alcohol (13) to the acid (14) was achieved via the aldehyde (PDC, CH_2Cl_2, 25°, 4 hr) and then ($AgNO_3$, 15%, KOH, H_2O, 3 hr) in 70% yield. The acid (14) was quantitatively converted to its methyl ester (15) by treating with ethereal diazomethane. Partial reduction of 15 to the diene 16 was successfully carried out by hydrogenation using Lindlar catalyst in pet.ether. The PMR and ^{13}C NMR of 16 were in agreement with the reported[5] data of the benzoate of methyl ester of 9-hydroxy-(E)-10(Z)-12-octadecadienoic acid. Saponification of 16 (3 eq. K_2CO_3, MeOH, H_2O (4:1), 25°, 12 hr) followed by careful acidification (MeOH, AcOH) afforded dimorphecolic acid (2) in 65% yield.

The above approach is being extended for the synthesis of other unsaturated hydroxy fatty acids[5] showing self defensive activity against rice blast disease.

Scheme-1


H — ≡ — H + Cl
NaNH2 , liq· NH3
H — ≡ OH
(3)
LiNH2, liq·NH3
Br-(CH2)7-CH2OTHP
(4)
LiNH2, liq·NH3
CH3(CH2)4-Br
THPOCH2-(CH2)7— ≡ OH
(5)
OH
(11)
1. MnO2, CHCl3
2. CH3(CH2)4-Br, Mg, ether
1. MnO2, CHCl3
2. Br-(CH2)7-CH2OTHP Mg, THF
OH
THPOCH2-(CH2)7— ≡
(6)
OH
(CH2)7-CH2 OTHP
(12)
1. PhCOCl, Py
2. PPTS, EtOH
1. PhCOCl, Py
2. PPTS, EtOH
OCOPh
HOCH2(CH2)7— ≡
(7)
OCOPh
(CH2)7-CH2OH
(13)
1. PDC, CH2Cl2
2. Alk., Ag2O
3. CH2N2
1. PDC, CH2Cl2
2. Alk., Ag2O
3. CH2N2
OCOPh
RO2C-(CH2)7— ≡
(8) R = H
(9) R = Me
OCOPh
(CH2)7CO2R
(14) R = H
(15) R = Me
H2, Lindlar catalyst
H2, Lindlar catalyst
CO2Me
OCOPh
(10)
PhOCO
CO2Me
(16)
K2CO3, MeOH-H2O
K2CO3, MeOH-H2O
±(1)
±(2)

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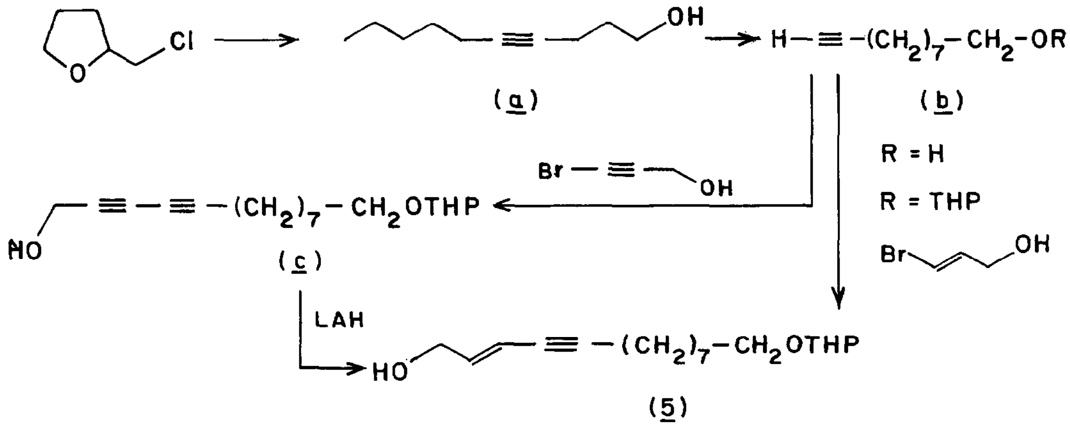
7 All the new compounds showed the spectral data consistent with the proposed structures and gave satisfactory elemental analyses.

8 Compound 5 was also made by two other approaches: The 4-decyn-1-ol(a), readily prepared in one operation from tetrahydrofuryl chloride, was converted to the terminal acetylenic alcohol (b) *via* acetylene Zipper reaction with $NaNH_2$ in 1,3-diaminopropane. The THP ether of b was then treated with 1.3 eq of (E)-3-bromoprop-2-en-1-ol, cuprous iodide (2 mole %) and *bis* (triphenylphosphine)-palladium dichloride (0.5 mole %) in diethyl amine at 40° to give 5 in 65% overall yield. In an alternate approach b was reacted with 3-bromopropargyl alcohol (1.2 eq) in presence of catalytic amount of cuprous chloride, hydroxylamine hydrochloride (Cadiot-Chodkiewicz reaction) to give the diacetylenic alcohol (c) which was converted to 5 by selective LAH reduction in ether.



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