104292-93-5; **7u**, 43154-87-6; **7v**, 104292-94-6; **10a**, 104293-02-9; **12a**, 62-53-3; **12b**, 100-46-9; **12c**, 64-04-0; **12d**, 100-61-8; **12e**, 103-67-3; **12f**, 110-89-4; **13a**, 103-84-4; **13b**, 588-46-5; **13c**, 877-95-2; **13d**, 579-10-2; **13e**, 10264-12-7; **13f**, 5827-78-1; **13g**, 34317-21-0; **13h**, 26209-45-0; **13i**, 1485-70-7; **13j**, 3278-14-6; **13k**, 776-75-0; **13l**, 104293-03-0; TBDMSCl, 18162-48-6; MEMCl, 3970-21-6; 4-$HOCH_2C_6H_4CO_2Me$, 6908-41-4; $MeOCH_2Cl$, 107-30-2; 4-$MOMOCH_2C_6H_4CO_2Me$, 104292-95-7; $MEMOCH_2C_6H_4CO_2Me$, 104292-96-8; 4-$THPOCH_2C_6H_4CO_2Me$, 104292-97-9; 4-$HOCH_2C_6H_4CO_2H$, 3006-96-0; 2-$MeO_2CCH_2C_6H_4CO_2Me$, 716-43-8; 2-$MeO_2CCH(Me)C_6H_4CO_2Me$, 104292-98-0; diethyl 3,3-(ethylenedioxy)glutarate, 86024-92-2; dihydropyran, 110-87-2; $PhCH_2Br$, 100-39-0; ethyl [3-(ethoxycarbonyl)-4-hydroxythiophene-2-yl]-acetate, 95421-56-0; ethyl [3-(ethoxycarbonyl)-4-methoxythiophene-2-yl]acetate, 104292-99-1; ethyl [4-(ethoxycarbonyl)-1,5-diphenylpyrazol-3-yl]acetate, 41470-68-2; methyl [5-methoxycarbonyl)pyrazol-4-yl]acetate, 104293-00-7; methyl [benzyl-5-(methoxycarbonyl)pyrazol-4-yl]acetate, 104293-01-8.

Short and Efficient Syntheses of Coriolic Acid

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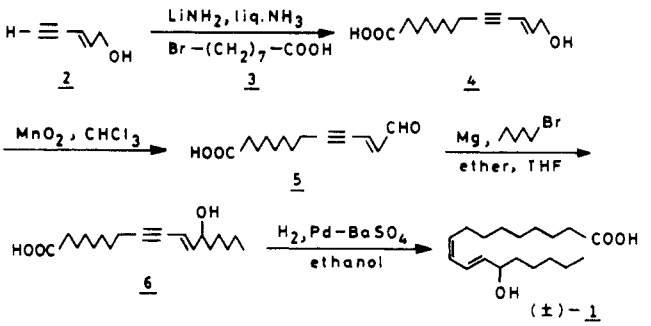
Coriolic acid (1), a divalent cation ionophore and a self-defensive substance against blast disease in rice plant, has been synthesized by two convenient approaches.

Coriolic acid (1)[1] belonging to a family of oxyoctadecadienoate congeners commonly found in vegetable oils was isolated from bovine heart mitochondria and shown to possess unique calcium-specific ionophoric activity.[2] Recently 1 was also isolated from *Fukuyuki* (*Oryza sative* L.) and demonstrated to act as self-defensive substance against rice blast disease.[3] Compound 1 is also present in sera of patients with familial Mediterranean fever (FMF) and may have a role in pathogenesis of FMF.[4] These findings prompted us to accomplish its synthesis so that its biological properties can be well assessed. Although two methods have been reported,[5,6] neither has been found suitable for the preparation of 1 in multigram quantities. In order to get coriolic acid (1) in substantial quantities for biological testing, we have developed two short and efficient methods for its synthesis. The common synthetic strategy in both the methods involved the alkylation of acetylenic alcohol with 8-bromooctanoic acid and stereoselective reduction of the acetylenic bond to a cis double bond.

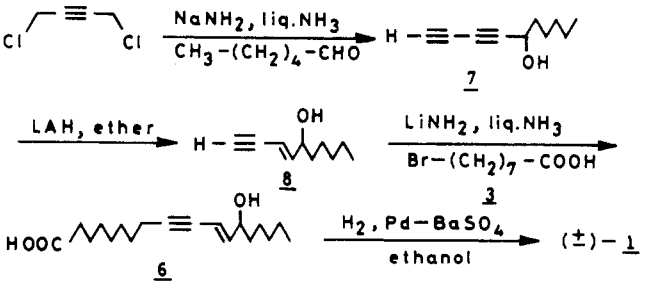
In the first approach (Scheme I) the synthesis of 1 centers around (*E*)-pent-2-en-4-yn-1-ol (2) which should facilitate the elaboration of aliphatic chain and allows the acetylenic bond to serve as a precursor for the cis double bond.

The key synthon (*E*)-pent-2-en-4-yn-1-ol (2) was made[7] by treating sodium acetylide with epichlorohydrin in liquid ammonia and usual workup. 2 on alkylation with 8-bromooctanoic acid (3, prepared from octane-1,8-diol) in the presence of lithium amide in liquid ammonia furnished the unsaturated hydroxy acid 4 in 85% yield. Oxidation of 4 with activated manganese dioxide in chloroform at room temperature afforded the acid aldehyde 5 in 60% yield. 5 was treated with *n*-pentylmagnesium bromide in THF to give the carbinol 6 in 75% yield. Compound 6 on partial hydrogenation with Lindlar catalyst in the presence of quinoline furnished coriolic acid (1) in 95% yield.

Scheme I



Scheme II



In an alternative approach (Scheme II) the synthesis of 1 starts with 1,3-butadiyne, which allows the aliphatic chain elaboration by successive alkynylation and alkylation reactions and serves as precursor for the stereoselective introduction of trans and cis double bonds.

Thus, 1,4-dichlorobut-2-yne on reaction with capronaldehyde in the presence of sodium amide in liquid am-

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monia[8] gave deca-1,3-diyn-5-ol (7). The diacetylenic alcohol 7 on selective reduction with lithium aluminum hydride in ether gave (*E*)-dec-3-en-1-yn-5-ol (8) in 45% overall yield. Not only does compound 8 possess the required *trans*-en-ol system but also the acetylenic bond will serve as a handle for chain elaboration. Thus, alcohol 8 on alkylation with 8-bromooctanoic acid (3) in the presence of lithium amide in liquid ammonia afforded the carbinol 6 in 70% yield, which is already converted to coriolic acid by partial hydrogenation in the presence of Lindlar catalyst.[9]

Although both approaches are notable for their simplicity, brevity, and apparent generality that enabled us to prepare coriolic acid (1) in gram quantities, the first approach is slightly superior as the intermediates involved are inexpensive and there are no scale up problems.

Experimental Section

Melting points are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded as Nujol mulls or neat on a Perkin-Elmer Model 683 spectrophotometer with sodium chloride optics. ^1H NMR spectra were obtained on a Varian T-60, a Varian FT-80A, or a Bruker WH-90 spectrometer in $CDCl_3$ or CCl_4 solutions containing Me_4Si as an internal standard with chemical shifts (δ) expressed (ppm) downfield from Me_4Si. Mass spectra were run on an AEI MS 30 double-beam mass spectrometer or CEC 21-110 B spectrometer. All solvents and reagents were purified and dried by standard techniques.

8-Bromooctanoic Acid (3). Octane-1,8-diol (11.68 g, 0.08 mol) was refluxed with 48% HBr (15.5 mL) in toluene for 6 h. The cooled reaction mixture was diluted with water, and the organic layer was washed with 10% $NaHCO_3$ solution and saturated brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was subjected for oxidation without further purification.

The crude 8-bromooctanol was treated with Jone's reagent in acetone. The excess of reagent was destroyed by the addition of 2-propanol, the reaction mixture was filtered, and the solvent was removed. The crude bromooctanoic acid was purified by the acid–base treatment to give pure 3 (7.15 g) in 42% yield: mp 38 °C; IR (Nujol) 3150 (COOH), 1710 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 1.2–1.9 (m, 10 H, 5 CH_2), 2.35 (t, 2 H, CH_2), 3.35 (t, 2 H, CH_2), 10.5 (br s, 1 H, COOH).

(*E*)-13-Hydroxytridec-9-yn-11-enoic Acid (4). To a freshly prepared suspension of lithium amide [prepared from 0.96 g (0.135 mol) of lithium] in liquid ammonia (125 mL) were added 2 (5.12 g, 0.0625 mol) in THF (20 mL) over a period of 15 min and a solution of bromo acid 3 (5.57 g, 0.025 mol) in THF (30 mL) during 25 min successively. The reaction mixture was allowed to stir at −33 °C for 10 h. Then, the cooling bath was removed, and the ammonia was allowed to evaporate. The residue was neutralized with dilute HCl and extracted with chloroform; extracts were washed with water and brine and dried (Na_2SO_4). The residue was purified by column chromatography (silica gel) to give 4 (4.75 g) as a solid in 85% yield (on the basis of bromo acid used): mp 65–66 °C; IR (Nujol) 3150 (OH, COOH), 1690 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 1.1–1.9 (m, 10 H, 5 CH_2), 2.1–2.5 (m, 4 H, 2 CH_2), 4.1 (d, 2 H, CH_2OH), 5.7 (d, 1 H, olefinic), 6.1 (dt, 1 H, olefinic). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.64; H, 8.92. Found: C, 69.68; H, 8.91.

(*E*)-13-Oxotridec-9-yn-11-enoic Acid (5). To a solution of 4 (4.48 g, 20 mmol) in chloroform (225 mL) was added activated manganese dioxide (40 g), and the resultant mixture was stirred at room temperature for 1.5 h. The reaction mixture was filtered and washed with chloroform and the filtrate concentrated to give the aldehyde 5 (2.66 g) in 60% yield as a solid: mp 51–52 °C; IR (Nujol) 3200 (br, COOH), 2100 (C=O), 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 10 H, 5 CH_2), 2.1–2.4 (m, 4 H, 2 CH_2), 6.0–6.6 (m, 2 H, olefinic), 9.5 (dd, 1 H, CHO), 10.0 (br s, 1 H, COOH). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.27; H, 8.10. Found: C, 70.52; H, 8.08.

(*E*)-13-Hydroxyoctadec-9-yn-11-enoic Acid (6). A solution of *n*-pentyl bromide (1.88 g, 12.5 mmol) in absolute 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 5 (1.11 g, 5 mmol) in THF (25 mL) was added dropwise and allowed to stir overnight. The mixture was poured into ice-cold aqueous ammonium chloride solution and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give 6 (1.10 g) in 75% yield as an oil: IR (neat) 3300 (br, COOH and OH), 2200 (C≡C), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (dist t, 3 H, CH_3), 1.1–1.8 (m, 18 H, 9 CH_2), 2.4 (m, 4 H, 2 CH_2), 4.1 (m, 1 H, $CHOH$), 5.6–5.8 (d, 1 H, olefinic), 5.9–6.1 (dd, 1 H, olefinic), 5.9 (br, 2 H, COOH and OH); mass spectrum, M^+ *m/e* 294. Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.48; H, 10.20. Found: C, 73.20; H, 10.22.

13-Hydroxy-9(*Z*),11(*E*)-octadecadienoic Acid (1). A mixture of hydroxy acid 6 (0.44 g, 1.5 mmol) and Lindlar catalyst (0.15 g) in ethanol (8 mL) containing 2 drops of quinoline was subjected to hydrogenation at atmospheric pressure. After the absorption of the required amount of hydrogen (33.6 mL), the suspension was filtered and washed with ethanol. Ethanol was evaporated from the filtrate. The residue obtained was dissolved in ether, washed with very dilute HCl and water, dried (Na_2SO_4), and evaporated to give 1 (0.42 g) in 95% yield as an oil: IR (neat) 3350 (OH and COOH), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (dist t, 3 H, CH_3), 1.2–1.8 (m, 18 H, 9 CH_2), 2.1–2.4 (m, 4 H, 2 CH_2), 4.1 (m, 1 H, $CHOH$), 5.5–6.3 (m, 6 H, 4 olefinic, OH, and COOH); mass spectrum, M^+ *m/e* 296. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.98; H, 10.81. Found: C, 72.90; H, 10.79.

Deca-1,3-diyn-5-ol (7). To a freshly prepared suspension of sodamide [prepared from 13.2 g (0.6 mol) of sodium] in liquid ammonia (400 mL) was added 1,4-dichlorobut-2-yne (24.6 g, 0.2 mol) very slowly with constant stirring. After 5 min caproaldehyde (20 g, 0.2 mol) in ether (100 mL) was added at −33 °C for 30 min. Stirring was continued for a further 4 h at this temperature, and then ammonia was allowed to evaporate, neutralized with aqueous NH_4Cl solution, and extracted with ether. The ether extracts were washed with brine, dried (Na_2SO_4), and concentrated to give crude 7, 21 g. Due to its rapid polymerization, distillation of 7 was not carried out: IR (neat) 3440 (OH), 3320 (HC≡C), 2220 (C≡C) cm^{-1}.

(*E*)-Dec-3-en-1-yn-5-ol (8). To the diacetylene alcohol 7 (15 g, 0.1 mol) in dry ether (150 mL) at 0 °C was added lithium aluminum hydride (3.8 g, 0.1 mol) in three portions. After 1 h it was brought to room temperature and stirred for 12 h. Then, it was poured over ice and extracted with ether; the ether extracts were washed with water and dried (Na_2SO_4). Evaporation of solvent gave a residue, which was purified by column chromatography (silica gel) to afford 8 (6.8 g) in 45% yield: IR (neat) 3440 (OH), 3320 (HC≡C), 2220 (C≡C), 960 (trans double bond); ^1H NMR ($CDCl_3$) δ 0.9 (dist t, 3 H, CH_3), 1.05–1.60 (m, 8 H, 4 CH_2), 2.8 (dt, 1 H, HC≡C), 4.1 (m, 1 H, $CHOH$), 5.5–6.25 (m, 2 H, olefinic); mass spectrum, M^+ *m/e* −152. Anal. Calcd for $C_{10}H_{16}O$: C, 78.95; H, 10.53. Found: C, 78.90; H, 10.51.

(*E*)-13-Hydroxyoctadec-9-yn-11-enoic Acid (6). To a freshly prepared suspension of lithium amide [prepared from 0.28 g (0.04 mol) of lithium] in liquid ammonia (100 mL) was added 8 (3.04 g, 0.02 mol) in THF (10 mL) over a period of 15 min. After 1 h of stirring at −33 °C, at solution of 8-bromooctanoic acid (2.2 g, 0.01 mol) in THF (10 mL) was added during 15 min. The reaction mixture was further stirred at −53 °C for 10 h. Afterward, ammonia was allowed to evaporate; the residue was neutralized with dilute hydrochloric acid and extracted with chloroform. The chloroform extracts were washed with water and brine and dried (Na_2SO_4). The residue was purified by column chromatography (silica gel) to afford 6 (2.05 g) in 70% yield).

Registry No. (±)-1, 73804-64-5; 2, 35042-52-5; 3, 17696-11-6; 4, 103621-51-8; 5, 103621-52-9; (±)-6, 103621-53-0; (±)-7, 103621-54-1; (±)-8, 103621-55-2; $HO(CH_2)_8OH$, 629-41-4; $Br(CH_2)_8OH$, 50816-19-8; $Br(CH_2)_4CH_3$, 110-53-2; $ClCH_2C{\equiv}CCH_2Cl$, 821-10-3; $H_3C(CH_2)_4CHO$, 66-25-1.

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