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SYNTHESIS OF 12(R),13(S)-OXIDO-9Z-OCTADECENOIC (VERNOLIC) AND 13(S)-HYDROXY-9Z,11E-OCTADECADIENOIC (CORIOLIC) ACIDS

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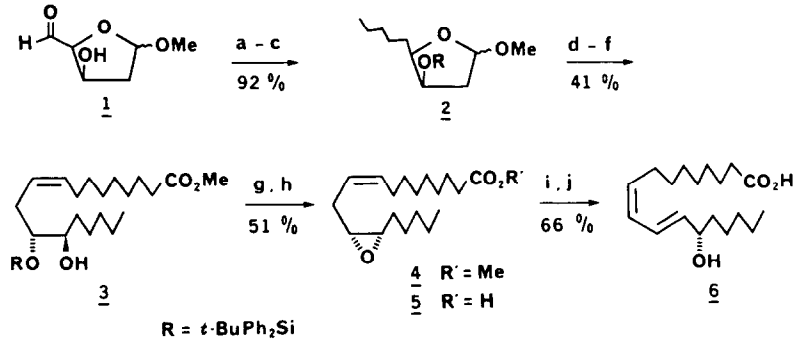
Summary: (-)-Vernolic acid was prepared enantiospecifically from a readily available carbohydrate precursor and isomerized to (+)-coriolic acid using the methylmagnesium salt of N-cyclohexylisopropylamine.

Recently, (-)-vernolic acid[1] (5) and (+)-coriolic acid[2,3] (6) have attracted considerable attention[4] as representatives of two isomeric classes of fatty acid metabolites which act as self defense substances in rice plants[5]. In addition, vernolic acid is a product of the microsomal cytochrome P-450 epoxygenase pathway[6] and thus may have a physiological role in mammals. Coriolic acid is present in heart mitochondria[7] as well as the sera of patients with familial Mediterranean fever[8] (FMF) and displays cation-specific ionophore activity[7]. As an aid to further pharmacological evaluation, we report the enantiospecific total synthesis of 5 and its conversion to 6.



(a)$BuPh_3PBr$,BuLi,THF/HMPA 4:1, -78°—>0°C, 12 h; (b) 5% Pd/C, 1 atm H_2, EtOAc, 1h; (c) KH,t-$BuPh_2SiCl$, THF, 12h; (d) HOAc/THF/H_2O 5:2:2, 60-65°C, 2h; (e) $HO_2C(CH_2)_8PPh_3Br$, $LiN(SiMe_3)_2$, THF/HMPA 4:1, -78°—>0°C, 12h; (f) CH_2N_2; (g) TsCl, Py, 34h; (h) Bu_4NF, THF, 12h; (i) NaOH, MeOH; (j) $PhCH_3$, MMA, 0°C, 3h.

Aldehyde 1, prepared[9] in ∿ 50% yield from 2-deoxyglucose, was elaborated to 2[10] by condensation with butyltriphenylphosphorane, catalytic reduction of the resultant olefin and silylation. Acidic lactol hydrolysis followed by union with the ylide derived from 8-carboxyoctyltriphenylphosphonium bromide (9-bromononanoic acid[11], Ph_3P, CH_3CN, 82°C) under cis-olefination conditions[9], extractive isolation and esterification (CH_2N_2) afforded 3 (TLC:SiO_2, CH_2Cl_2, R_f ∿ 0.37) which was transformed to 4 by tosylation and exposure to fluoride anion; NMR($CDCl_3$, 90 MHz):δ 0.92(t,3H), 1.14-1.84 (m, 21H), 1.88-2.48 (m,6H), 2.82-3.09 (m, 2H), 3.67 (s, 3H), 5.23-5.70 (m, 2H); TLC:SiO_2, Et_2O/hexane 1:1, R_f ∿ 0.55; MS(CH_4): m/e 311, 293, 279; $[\alpha]_D^{24}$ -2.0° (c 2.7, $CHCl_3$).

Saponification of 4 furnished 5 (TLC:SiO_2, 10% MeOH/CH_2Cl_2, R_f ∿ 0.40) which was smoothly isomerized[12] to 6 using 4 equiv of the methylmagnesium derivative of N-cyclohexylisopropylamine[13] (MMA); NMR ($CDCl_3$, 90 MHz):δ 0.88 (t,3H), 1.05-1.76 (m, 18H), 1.90-2.30 (m, 2H), 2.34(t, J ∿ 7 Hz, 2H), 4.17 (q, J ∿ 6Hz, 1H), 5.43 (dt, J ∿ 7.5 and 10.5 Hz, 1H), 5.65 (dd, J ∿ 7 and 15 Hz, 1H), 5.97 (dd, J ∿ 11 and 11 Hz, 1H), 6.02 (br s, 1H), 6.50 (dd, J ∿ 11 and 15 Hz, 1H); TLC:SiO_2, 10% MeOH/CH_2Cl_2, R_f ∿ 0.35. Methyl ester of 6:$[\alpha]_D^{23}$ + 6.1° (c 0.98, $CHCl_3$), lit.[4b] $[\alpha]_D^{24}$ + 6.0° (c 1.6, hexane).

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