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A NOVEL CHEMO-ENZYMATIC ENANTIOSPECIFIC SYNTHESIS OF (S)-CORIOLIC ACID MEDIATED VIA IMMOBILIZED ALCOHOL DEHYDROGENASE OF BAKER'S YEAST

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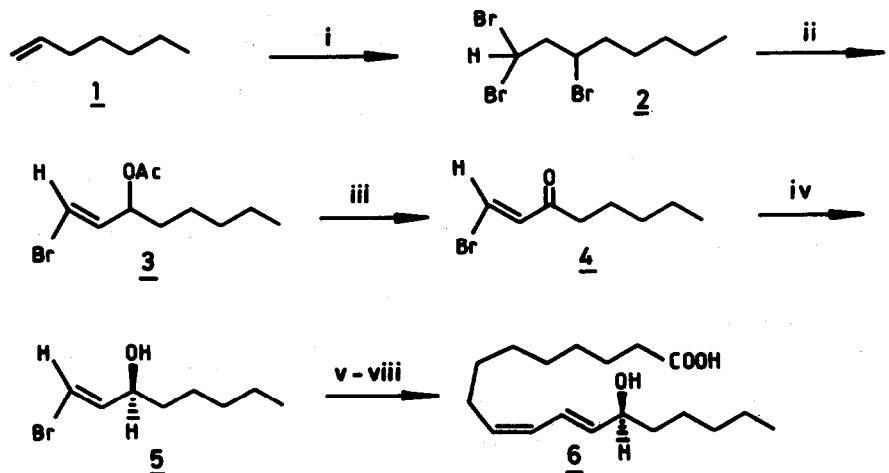
Abstract: (S)-(E)-(+)-1-Bromo-1-octene-3-ol was prepared in 85% yield and high optical purity (e.e. 97.4%) via a stereospecific reduction of corresponding bromo vinyl ketone using alcohol dehydrogenase from baker's yeast (EC 1.1.1.1) and NAD(P)H immobilized on Nucleosil 120-5 C_{18}, and converted to 13(S)-hydroxy-9Z,11E-octadecadienoic (coriolic) acid.

13(S)-Hydroxy-9Z,11E-octadecadienoic (coriolic) acid 6 is an oxygenated unsaturated fatty acid formed as a product of metabolism of linoleic acid in plants and animals[1], and possesses interesting biological activities[2]. Recently its synthesis has attracted considerable attention[3] as it was found to act as a self defence substance in rice plants[4]. Herein we report a short and simple enantiospecific synthesis of 6 following the pathway depicted in scheme I. The chiral bromo vinyl alcohol 5 is the key target in the synthesis of (S)-coriolic acid. However, reduction of α,β-unsaturated ketones such as 4 with whole cells to alcohol 5 is difficult[5] and mostly leads to reduction of double bond instead of keto function or reduction of both[3a]. We found that enzyme alcohol dehydrogenase from baker's yeast (E.C. 1.1.1.1) reduces 4 enantioselectively to (S)-5 keeping the bromo vinyl group intact in presence of NAD(P)H as cofactor.



SCHEME - I

Scheme I: i) Cu, $CHBr_3$; ii) KOAc (2 eq.), 18-crown-6, DMF; iii) K_2CO_3/MeOH, then PCC; iv) ADH from baker's yeast and NAD(P)H immobilized on Nucleosil 120-5 C_{18}, ethyl acetate-isooctane 1:9, isopropanol, pH 7.5; v) H-C≡C-$(CH_2)_7$-COOMe, $Pd(PPh_3)_4$, CuI, Pr^nNH_2; vi) H_2-Pd; $BaCO_3$; vii) K_2CO_3-MeOH; viii) H^+.

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Our attempts to use Klibanov's methodology of enzyme immobilized on glass beads - substrate in ethyl acetate 6 were not successful, prompting us to look for an alternative methodology. We have successfully exploited the property of Nucleosil C18 of absorbing both hydrophilic as well as hydmphobic compounds to bring together the enzyme, the coenz~me NAD(P)H and the highly hydrophobic substrate tt. Recycle of the oxidized coenzyme NAD(P) is achieved by insitu enzymatic oxidation of isopropanol to acetone and consequent reduction of NAD(P) to NAD(P)H.

Copper catalysed brornoforrn addition to commercially available l-heptene 1 gave 3-brorno=l,l=dibrornooctane 2 (82%) which on treatment with two equivalents of potassium acetate lg-crown-6 in dime~hyl for marnide resulted in 3-acetoxy-l-brorno-l-octene 3 (85%). Hydrolysis of 3 in methanol-potassium carbonate and oxidation with pyridiniurn chlorochromate (PCC) gave exclusively (E)-ketovinylbrornide 4 (75%). This was enantiospecifically reduced 7 to (S) (E)-(+)-l-brorno-l-octen-3-ol g 5, (85%) with 97.4% e.e. as determined by its Mosher)s ester. 5 was coupled with methyl 9-decynoate in presence of Pd(PPh3)#, Cul and n-propyl amine 9. The product (58%) on partial hydrogenation over palladium on barium carbonate furnished exlclusively cis-hydrogenated 9E,IIZ methyl ester (80%) which was hydrolysed to (S)-coriolic acid 10 6 **(85%).**

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7. In a typical experiment the enzyme (5 rng,Sigrna,USA) and NAD(P)H (15 rng,20~ moles, Spectrochem, India) were dissolved in iris buffer (5 mL, 0.05 M, pH *7.5)* and mixed with Nocleosil 120-5 C.^ (3g). The slurry was air dried for 6-8 hrs and stirred with solution of tt (205 rag, I rnmo~e~ in ethyl acetate-isooctane (1:9, 50 rnL) at r.t. Isopropanol (4rnL) was added in aliquots of 200~t over 5 days. The reduction was co rnplete in one week as followed by t.l.c. Filtration and column chromatography yielded 5 (175 rng, 85%) with e.e. 97.4% as determined by its Musher ester.
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I0. *H NMR (200 MHz, CdCI3): 4 ~fO.91 (t,3H,Me), 1.2-1.6 (br,s,6H,3CH2)' 2.50 (t,2H,COCH~, 6.80 (d, 3=I~I-iZ,IH~=CHBr), *7.55* (d,3=I4.Hz, IH,=CHCO), 5 ~)~+12.7°(c 1.39,metha~, e.e.97.4%, ii~ {'-~)~for (5)5 + 13.1° (c 1.39, CHC13),~0.92 (t, 3=7.2Hz,3H,MeJ, 1.25-1.75 (br,s,gH,4CH~ ,, 1.94 (s, IH,OH), 4.12 (~,IH,CHOH), 6.0-6.4 (rrb2H, -:CH), 61"~9.1 (c 1.29 • CHCl~), 1it.~.,~+9.3 (c 1.29 CHCI~). H NMR (200 MHz, CDCl)$0 91 (t,3H,3-7 2Hz Me) [1].05=I'.75 (Ix~'~'I-gH,gCH~), 1.91-2.12f (rn,2H,CH~-CH=CH), 2.32 (t,~H,C~oCOOH), 4.12 (rrblH,[9] C~[OH), 4.71(br s,1H, O'l-l), 5.13-6.15 (rrb3H,C~-I=CH-CH=CH-CHOH), 6".42 (dd, 3=9.g and 15Hz,IH, =CH), 9.7g (br s, IH,COOH).

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