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STEREOSELECTIVE SYNTHESIS OF (9Z,15Z)-(11S,12S,13S)-11-HYDROXY-12,13-EPOXY OCTADECADIENOIC ACID : A CONSTITUENT OF RICE PLANT INFECTED WITH RICE BLAST DISEASE

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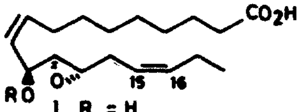
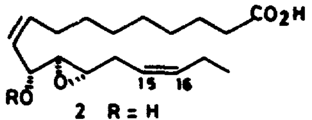
Summary : *An elegant, stereoselective synthesis of (9Z,15Z)-(11S,12S,13S)-11-hydroxy-12,13-epoxy octadecadienoic acid (1) by enantioselective epoxidation is described.*

In recent times several kinds of oxygenated unsaturated fatty acids have been isolated from the resistant cultivar variety of rice plant such as Fukuyuki against rice blast disease[1]*. These fatty acids are produced by the plant as self defensive substances against the fungus causing rice blast disease. Even the susceptible variety of rice plant such as Sasanishiki becomes resistant to the fungus when the roots of the plant are soaked for few days in dilute solutions of these acids in water before plantation. Because of the role these fatty acids play in protecting the rice plant against rice blast disease, we have indulged in their total syntheses*[2a,b] *to prepare them in gram quantities so that their physiological properties can be assessed. To understand the genesis of the self defensive substances produced in the plant, Kato and his coworkers*[3] *studied the constituents of the infected rice plants and isolated several oxygenated fatty acids including epoxy acids 1-4, which show strong spore germination inhibitory action against rice blast diseases.*



1 R = H
3 R = H , 15 , 16 dihydro
5 R = p-Br-C$_6$H$_4$-$\overset{\text{O}}{\overset{\|}{\text{C}}}$-



2 R = H
4 R = H , 15 , 16 dihydro

We wish to report herein the first total synthesis of (9Z,15Z)-(11S,12S,13S)-11-hydroxy-12,13-epoxy octadecadienoic acid (1). Our strategy for the synthesis of the epoxy benzoate **10** *(Scheme 1) is based on our recent study*[4] *on the Sharpless Kinetic resolution of racemic allyl propargyl alcohols by enantioselective epoxidation.*

Thus, our desired allyl propargyl alcohol (8) required for the present synthesis was prepared by the lithiation of 8-tetrahydropyranyloxy-1-octyne (6) with n-BuLi and subsequent quenching of the anion with (2E)-octen-5-yn-1-al[5] *(7) in good yield. Sharpless kinetic resolution was carried out as follows: in a single necked round bottomed flask fitted with a serum cap, anhydrous dichloromethane was taken and cooled to -23°C. To it titanium tetraisopropoxide (1 eq.) was added and stirring continued for 5-10 min before the next addition of (+) diisopropyl tartrate (1 eq.). Allyl propargyl alcohol* **8** *(1 eq.) was added and then t-butyl hydroperoxide (90%, 0.6 eq.), an interval of 5-10 min was maintained between each addition. The resulting homogenous solution was stored in a freezer (-23°C). The progress of the reaction was monitored by titrating the remaining TBHP and the reaction was quenched after the near*

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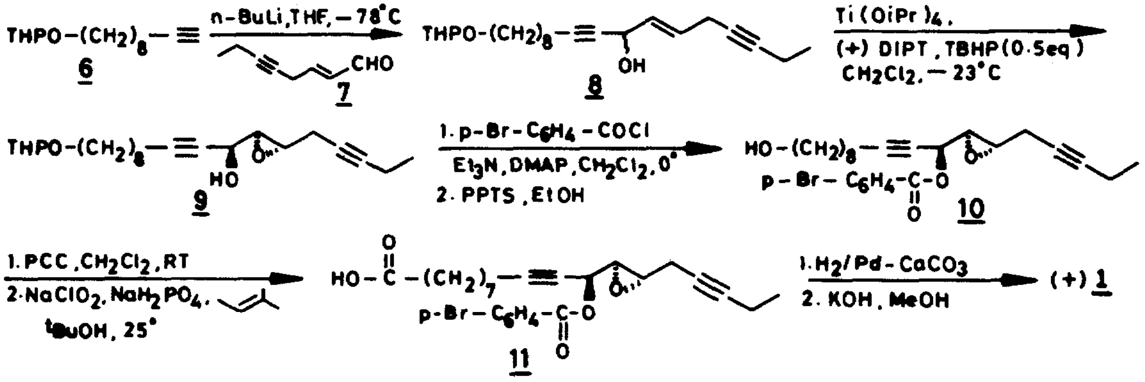
consumption (≃ 90%) of TBHP was observed. The usual chromatography led to the isolation of optically pure epoxy alcohol **9** and allyl propargyl alcohol **8**. The secondary alcohol of **9** was protected as its p-bromo benzoate (p-bromobenzoyl chloride, Et_3N, DMAP in dichloromethane at 0°C) and the tetrahydropyranyl ether was cleaved using PPTS/ethanol to give alcohol **10** $[\alpha]_D$ -19.2° (c 0.26, $CHCl_3$). Our next task was to achieve the oxidation of the primary alcohol **10** to the corresponding acid without affecting the very sensitive epoxide and acetylenic functionalities, and was accomplished successfully in stepwise manner employing mild reagents. For instance, **10** was oxidised first to aldehyde using $PCC\text{-}CH_2Cl_2$ and then to the acid **11** using $NaClO_2$, NaH_2PO_4 and 2-methyl-2-butene in ^{t}BuOH-water (5:2) at ambient temperature in 70% yield{ $[\alpha]_D$ -13.5° (c 0.7, $CHCl_3$)}.

Scheme – 1



Partial hydrogenation of acetylenic moiety in **11** over Lindlar catalyst gave **5**[6] $[\alpha]_D$ -38.9° (c 0.59, $CHCl_3$), lit.[3] $[\alpha]_D$ -41.2° (c 0.13, $CHCl_3$). **5** on treatment with 0.25% methanolic KOH (2.2 eq.) produced title compound (**1**) $[\alpha]_D$ +39.49° (c 0.79, $CHCl_3$) whose methyl ester was identical in all respects with the reported data[3]. The recovered allyl propargyl alcohol **8** has been recycled[7a] by inverting the hydroxyl group using Mitsunobu reaction[7b] (i DEAD, TPP, Φ-COOH, ii KOH/MeOH) and performing epoxidation as described above to give the epoxy alcohol **9**.

The synthetic approach reported herein for the synthesis of **1** in optically pure form appears to be very practical and general. This procedure may be adopted for the synthesis of several physiologically active compounds having structures similar to these oxygenated fatty acids.

References

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2. a) A.V. Rama Rao, E.R. Reddy, G.V.M. Sharma, P. Yadagiri and J.S. Yadav, Tetrahedron Lett., **26**, 465 (1985); b) A.V. Rama Rao and E.R. Reddy, Tetrahedron Lett., **27**, 2279 (1986).
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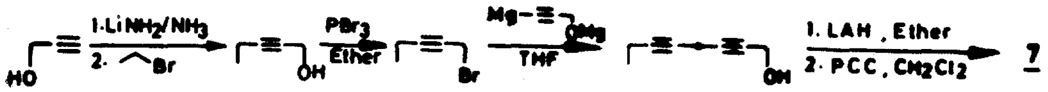
5. (2E)-Octen-5-yn-1-al (**7**) is prepared as follows:



6. All new compounds gave expected spectroscopic data and satisfactory elemental analysis.
7. a) A.V. Rama Rao, J.S. Yadav, K. Bal Reddy and A.R. Mehendale, J. Chem. Soc. Chem. Commun., 453 (1984); b) O. Mitsunobu, Synthesis, 1 (1981).

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