ENANTIOCONTROLLED SYNTHESIS OF (11*S*,12*S*,13*S*)-(9*Z*,15*Z*)- AND (11*R*,12*S*,13*S*)-(9*Z*,15*Z*)-11-HYDROXY-12,13-EPOXY OCTADECADIENOIC ACIDS BY MEANS OF THE SHARPLESS ASYMMETRIC EPOXIDATION OF THE UNSYMMETRICAL DIVINYLCARBINOL

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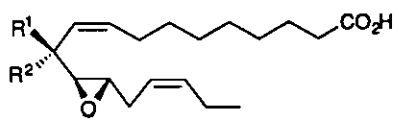
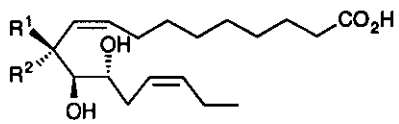
Abstract -- (11*S*,12*S*,13*S*)-(9*Z*,15*Z*)- and (11*R*,12*S*,13*S*)-(9*Z*,15*Z*)-11-Hydroxy-12,13-epoxy octadecadienoic acids, self defensive substances against the rice blast disease, were synthesized enantioselectively by employing the Sharpless asymmetric epoxidation reaction of the unsymmetrical divinylcarbinol, as a key step.

Several oxygenated metabolites of unsaturated C_{18} fatty acids, such as the compounds (**1-4**), were isolated by Kato and co-workers[1] from the rice plants suffering from rice blast caused by *Pyricularia oryzae*. These fatty acids were shown to be self-defence substances against the fungus. For example, the epoxy compounds (**1**) and (**2**) exhibit strong spore germination inhibitory action against the rice blast disease. Owing to their interesting biological activity and also to their low abundance in natural sources, much effort has been devoted to develop



1 R^1 = OH, R^2 = H
2 R^1 = H, R^2 = OH



3 R^1 = OH, R^2 = H
4 R^1 = H, R^2 = OH

Figure 1.

This paper is dedicated to the memory of the late Professor Shun-ichi Yamada.

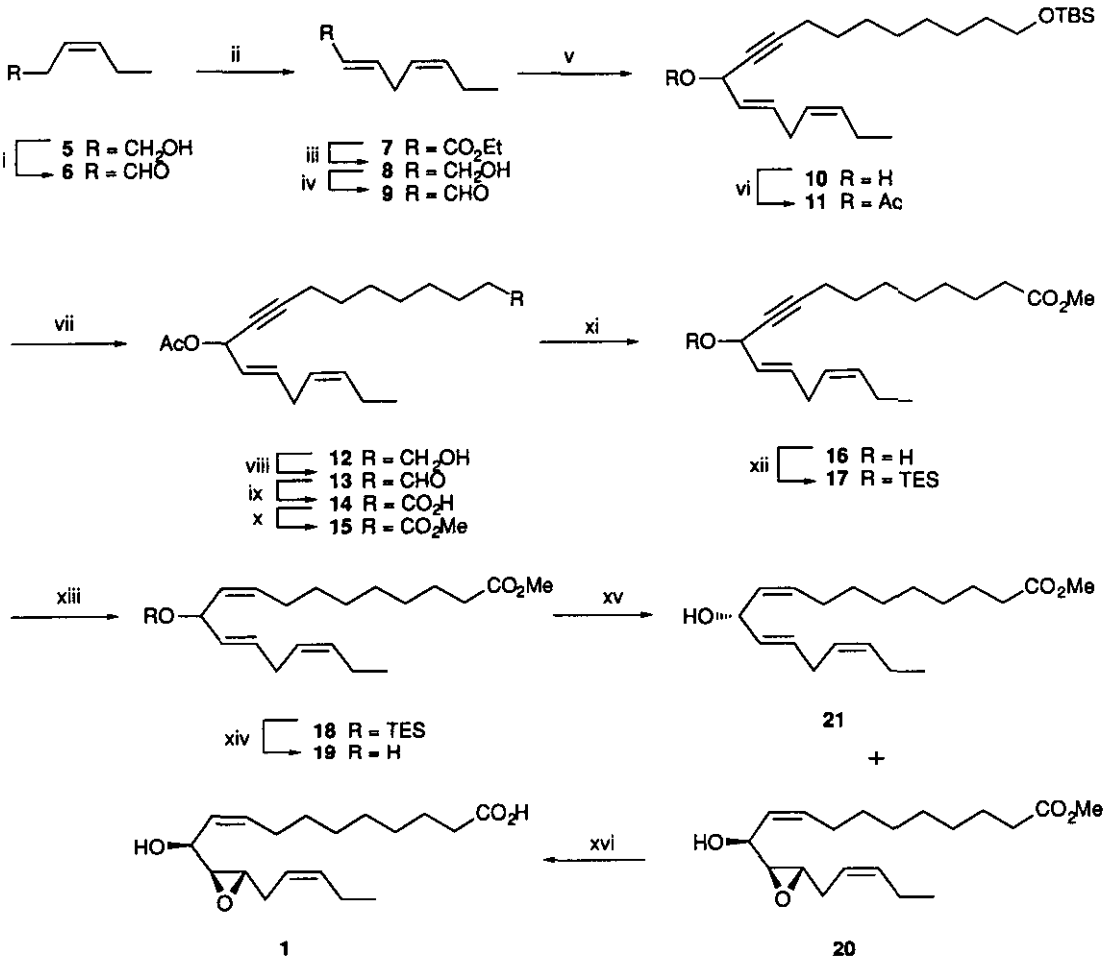
an efficient procedure for their syntheses.[2]

Recently we have established the Sharpless asymmetric epoxidation reaction of racemic unsymmetrical divinylcarbinols, where the kinetic resolution and subsequent epoxidation have proceeded in an entirely regio- and diastereoselective manner to give the corresponding epoxy-alcohols with high emantiomeric excesses.[3,4] This procedure has already been applied to the enantioselective synthesis of an antitumor antibiotic, (+)-asperlin, successfully.[3] As an extention of this work, we became interested in an enantioselective synthesis of (11*S*,12*S*,13*S*)-(9*Z*,15*Z*)- and (11*R*,12*S*,13*S*)-(9*Z*,15*Z*)-11-hydroxy-12,13-epoxy octadecadienoic acids, self defensive substances against the rice blast disease, since these natural products seem to be suitable target compounds for applying the above synthetic strategy.

The requisite unsymmetrical divinylcarbinol (**19**) was synthesized as follows. Dess-Martin periodinane oxidation[5] of (*Z*)-3-hexen-1-ol (**5**) gave (*Z*)-3-hexenal (**6**), which on Wittig-Horner reaction with triethyl phosphonoacetate afforded the dienoate (**7**). Reduction of the ester (**7**) with diisobutylaluminum hydride (DIBAL), followed by Dess-Martin periodinane oxidation of the alcohol (**8**) gave the dienal (**9**) in 69% yield. Addition of the lithium salt of 10-*tert*-butyldimethylsiloxy-1-decyne[6] to the aldehyde (**9**) gave the alcohol (**10**) in 83% yield. After protection of the secondary hydroxy group of **10** as the acetate (**11**), the silyl ether was removed by treatment with tetrabutylammonium fluoride (TBAF) to provide the primary alcohol (**12**) in 92% yield from **10**. Successive oxidation of the alcohol (**12**) with Dess-Martin periodinane reagent and sodium chlorite[7] gave the acid (**14**) *via* the aldehyde (**13**) in 89% yield from **12**. Esterification of the acid (**14**) with iodomethane and potassium carbonate afforded the ester (**15**), which was further converted into the triethylsilyl ether (**17**) by two steps involving methanolysis giving the alcohol (**16**) and silylation with triethylsilyl chloride (TESCl). The formation of the (*Z*)-olefin from the silyl ether (**17**) was achieved in a usual manner by using a catalytic reduction with the Lindlar catalyst to give the triene (**18**). Deprotection of the silyl group of **18** with TBAF afforded the alcohol (**19**) in 89% yield from **14**. With the requisite starting unsymmetrical divinylcarbinol (**19**) available, a study was made of the best conditions for the Sharpless asymmetric epoxidation to the desired epoxy-alcohol. The reaction of **19** with 0.4 equiv. of *tert*-butyl hydroperoxide (TBHP), 0.55 equiv. of L-(+)-DIPT and 0.5 equiv. of $Ti(O^iPr)_4$ in dichloromethane in the presence of calcium hydride and molecular sieves 3A at -40°C gave the epoxy-alcohol (**20**) and the recovered (*R*)-secondary alcohol (**21**), in 33% and 57% yields, respectively. None of the other products including the regioisomeric epoxide could be isolated in this reaction. The spectroscopic data including specific rotation, {$[\alpha]_D$ +69.6° ($CHCl_3$), lit.,[2h] $[\alpha]_D$ +72.2° ($CHCl_3$)}, of the former epoxide (**20**) were identical with those reported,[2h] suggesting its

absolute configurations to be 11*S*,12*S*, and 13*S*. Its enantiomeric excess was also determined to be 94% by HPLC analysis with the chiral column CHIRALPAK AD.

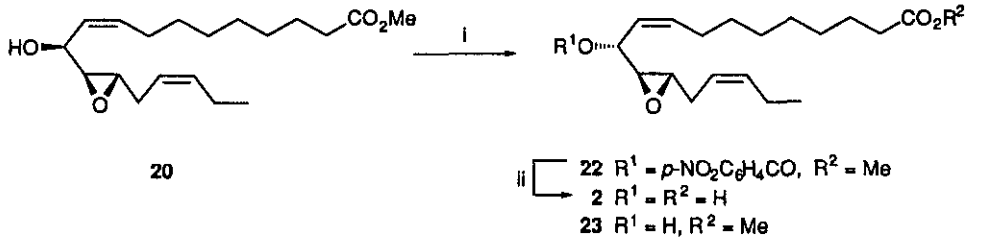
It should be noted again that the kinetic resolution and subsequent epoxidation of **19** under the Sharpless asymmetric oxidation conditions proceeded in an entirely regio- and diastereoselective manner.



Scheme 1. *Reagents and conditions*: i, Dess-Martin oxidation; ii, $(EtO)_2P(O)CH_2CO_2Et$, *n*BuLi, THF, 0°C; iii, DIBAL, THF, 0°C; iv, Dess-Martin oxidation; v, 10-*tert*-butyldimethylsiloxy-1-decyne, *n*BuLi, THF-HMPA, -40°C; vi, Ac_2O, pyridine, CH_2Cl_2; vii, TBAF, THF, 0°C; viii, Dess-Martin oxidation; ix, $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *tert*-BuOH-H_2O (4:1), rt; x, MeI, K_2CO_3, DMF, rt; xi, K_2CO_3, MeOH, rt; xii, TESCl, imidazole, CH_2Cl_2, rt; xiii, Pd-$CaCO_3$, H_2, pyridine, hexane, rt; xiv, TBAF, THF, rt; xv, L-DIPT, $Ti(O^iPr)_4$, TBHP (0.4 equiv.), CaH_2, MS3A, CH_2Cl_2, -40°C; xvi, 0.5N NaOH, THF, 0°C.

Finally, hydrolysis of the ester (**20**) with 0.5N sodium hydroxide afforded the desired acid (**1**), {$[\alpha]_D$ +65.2° ($CHCl_3$), lit.,[2a] $[\alpha]_D$ +39.5° ($CHCl_3$)}, in 91% yield. The reported value of rotation for the natural product[2a] was much smaller than that for our synthetic compound, possibly due to sample contamination.

(11*R*,12*S*,13*S*)-(9*Z*,15*Z*)-11-Hydroxy-12,13-epoxy octadecadienoic acid (**2**), $[\alpha]_D$ -54.2° ($CHCl_3$), was also synthesized from the epoxy-alcohol (**20**) by two steps, including Mitsunobu reaction with *p*-nitrobenzoic acid, and hydrolysis of the resulting *p*-nitrobenzoate (**22**) with lithium hydroxide, in 45% overall yield. The partial hydrolysis of **22** under the above reaction conditions with a shorter reaction time gave the hydroxy ester (**23**), {$[\alpha]_D$ -52.3° ($CHCl_3$), lit.,[2e] $[\alpha]_D$ -79.5° ($CHCl_3$)}, which was also converted into the acid (**2**).



Scheme 2. *Reagents and conditions*: I, DEAD, Ph_3P, *p*-$NO_2C_6H_4CO_2H$, Tol, -20°C; ii, LiOH, aqueous THF, rt.

The present work illustrates a further application of the Sharpless asymmetric epoxidation of the unsymmetrical divinylcarbinols to the synthesis of physiologically active fatty acids with high optical purity. The synthesis of the triols (**3** and **4**) by the ring-opening reaction of the epoxy-alcohols (**1** and **2**) is under investigation.

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